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Fifth Edition

Parasitic Diseases

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21. *Trichinella spiralis* (Railliet 1896)

Introduction

The genus *Trichinella* has undergone revision, due to the advent of reliable DNA probes that can be used to distinguish the various species that have been recently described.^{1,2} There are 8 recognized genotypes (two are provisional).³ Members of the genus *Trichinella* are able to infect a broad spectrum of mammalian hosts, making them one of the world's most widely-distributed group of nematode infections. *Trichinella spp.* are genetically related to *Trichuris trichiura* and *Capillaria spp.*; all belong to the family Trichurata. These roundworms constitute an unusual group of organisms in the phylum Nematoda, in that they all live a part of their lives as intracellular parasites.

The diseases that *Trichinella spp.* cause are collectively referred to as trichinellosis. Currently, prevalence of trichinellosis is low within the United States, occurring mostly as scattered outbreaks,⁴ and the majority of human cases are due to *Trichinella spiralis* and *T. murrelli*. The domestic pig is the main reservoir host for *T. spiralis*. This species is significantly higher in prevalence in people living in certain parts of Europe, Asia, and Southeast Asia than in the United States. It is now considered endemic in Japan and China. A large outbreak of trichinellosis occurred in Lebanon in 1997, infecting over 200 people.⁵ *Trichinella spiralis* infection in humans has been reported from Korea for the first time.⁶ In contrast, trichinella infections in wildlife within the United States are now thought to be largely due to the T5 strain, tentatively designated *T. murrelli*.⁷

An outbreak of *T. pseudospiralis* in Thailand has been reported.⁸ This species can also infect birds of prey. Foci have also been described in Sweden,⁹ The



Figure 21.1. Infective first stage larva of *Trichinella spiralis* in its Nurse cell in muscle tissue. The worm measures 1mm x 36 µm.

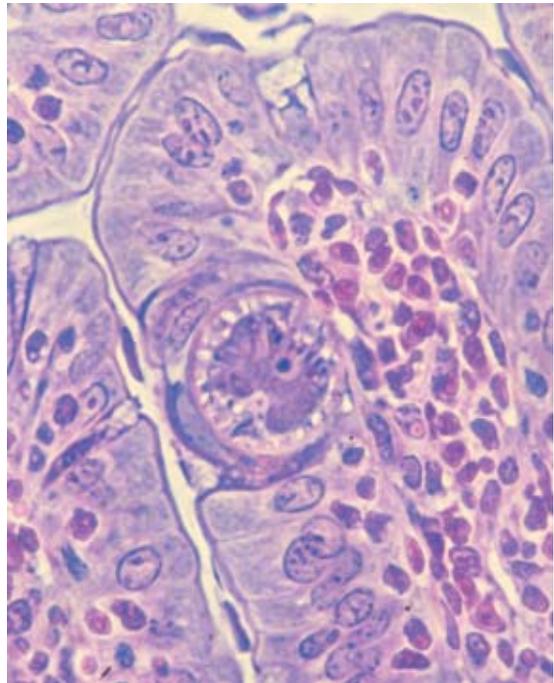


Figure 21.2. Adult *T. spiralis* in situ. Small intestine of experimentally infected mouse. The worm is embedded within the cytoplasm of the columnar cells.

Slovak Republic,¹⁰ and Tasmania (Australia).¹¹ *Trichinella paupae* (provisional), apparently similar in biology to *T. pseudospiralis*, has been described in wild and domestic pigs in Papua New Guinea.¹²

Humans can also be infected with *T. nativa* and *T. britovi*.^{13,14} Reservoir hosts for *T. nativa* include sled dogs, walruses, and polar bears. *T. britovi* is the sylvatic form of trichinellosis throughout most of Asia and Europe. There are numerous reports in the literature of infections with this parasite in fox, raccoon, dog, opossum, domestic and wild dogs, and cats.

T. nelsoni is restricted to mammals in Equatorial Africa, such as hyenas and the large predatory cats.¹⁵ Occasionally people acquire infection with *T. nelsoni*. Most animals in the wild, regardless of their geographic location, acquire trichinella by scavenging. The recently discovered *T. zimbabwensis* infects crocodiles and mammals in Africa, and is a non-encapsulate species.¹⁶ No human cases have been reported, so far. Puerto Rico and mainland Australia remain trichinella-free. *T. pseudospiralis* has been isolated from the Tasmanian Devil, but not from humans living in that part of Australia.¹¹ For an accounting of the history of the discovery of *Trichinella spiralis*, see www.trichinella.org/history_1.htm and www.trichinella.org/index_ppt.htm.

Life Cycle

Infection is initiated by ingesting raw or under-

cooked meats harboring the Nurse cell-larva complex (Fig. 21.1). Larvae are released from muscle tissue by digestive enzymes in the stomach, and then locate to the upper two-thirds of the small intestine. The outermost cuticular layer (epicuticle) becomes partially digested.^{17,18} This enables the parasite to receive environmental cues¹⁹ and to then select an infection site within the small intestine. The immature parasites penetrate the columnar epithelium at the base of the villus. They live within a row of these cells, and are considered intra-multi-cellular organisms (Figs. 21.2, 21.7).²⁰

Larvae molt four times in rapid succession over a 30-hour period, developing into adults. The female measures 3 mm in length by 36 μm in diameter (Fig. 21.3), while the male measures 1.5 mm in length by 36 μm in diameter (Fig. 21.4).

Patency occurs within five days after mating. Adult females produce live offspring — newborn larvae (Fig. 21.5) — which measure 0.08 mm long by 7 μm in diameter. The female produces offspring as long as host immunity does not develop. Eventually, acquired, protective responses interfere with the overall process of embryogenesis and creates physiological conditions in the local area of infection which forces the adult parasites to egress and relocate further down the intestinal tract. Expulsion of worms from the host is the final ex-



Figure 21.3. Adult female *T. spiralis*. 3 mm x 36 μm . Note fully formed larvae in uterus.

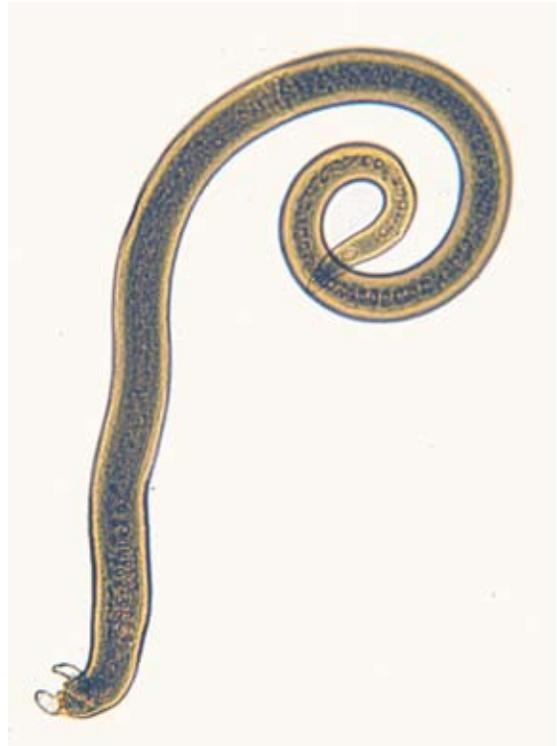


Figure 21.4. Adult male *T. spiralis*. Note claspers on tail (lower end). 1.5mm x 36 μm .

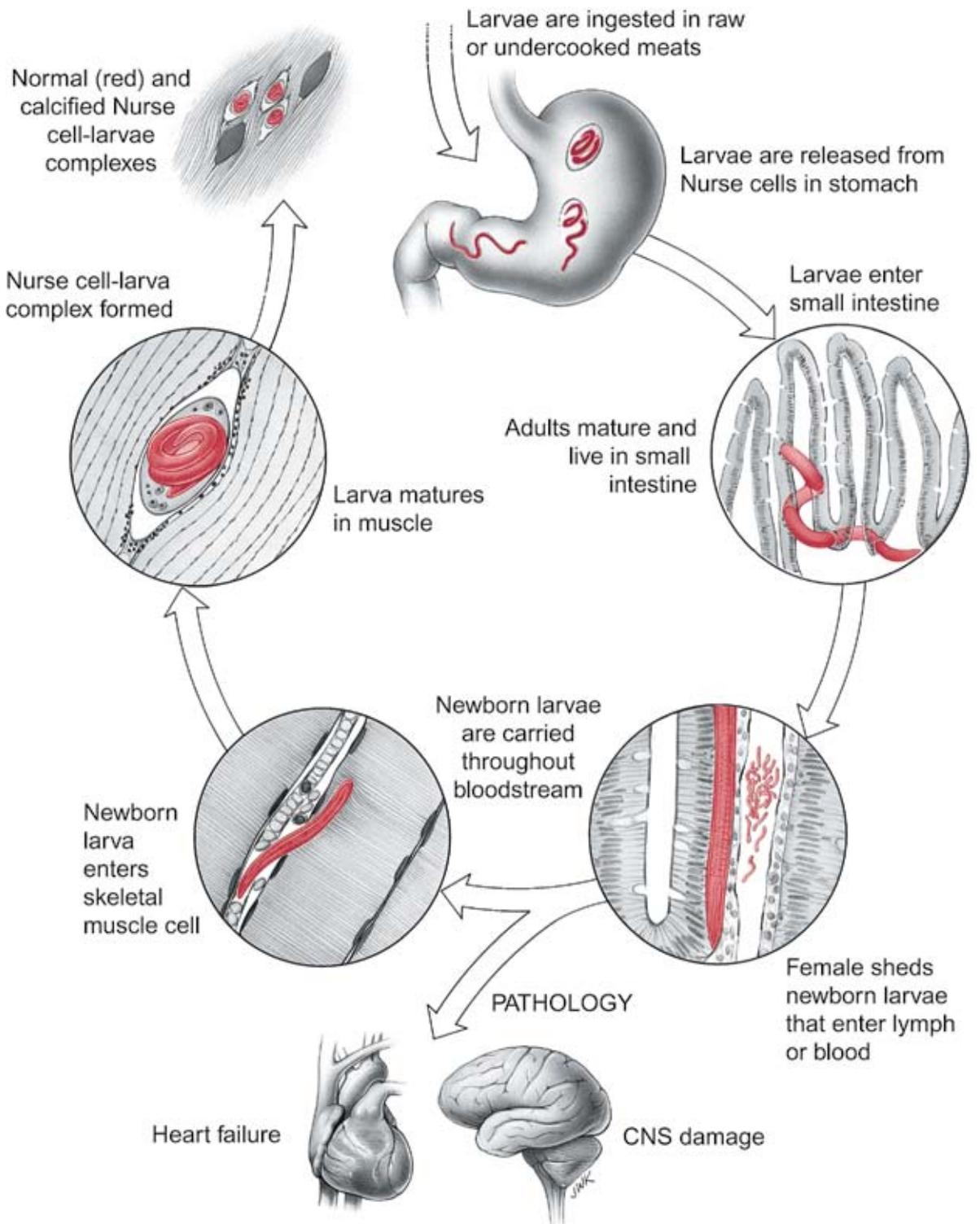
pression of immunity, and may take several weeks.

The newborn larva is the only stage of the parasite that possesses a sword-like stylet, located in its oral cavity. It uses it to create an entry hole in potential host cells. Larvae enter the lamina propria in this fashion, and penetrate into either the mesenteric lymphatics or into the bloodstream. Most newborn larvae enter the general circulation, and become distributed throughout the body.

Migrating newborns leave capillaries and enter cells (Fig. 21.6). There appears to be no tropism for any particular cell type. Once inside, they can either remain or leave, depending upon environmental cues (yet to be determined) received by the parasite. Most cell types die as the result of invasion. Skeletal muscle cells are the only exception. Not only do the parasites remain inside them after invasion, they induce a remarkable series of changes, causing the fully differentiated muscle cell to transform into one that supports the growth and development of the larva (Figs 21.8, 21.9). This process is termed Nurse cell formation.²¹ Parasite and host cell develop in a coordinated fashion. *T. spiralis* is infective by the 14th day of infection, but the worm continues to grow in size through day 20.²² The significance of this precocious behavior has yet to be appreciated.

Parasites inside cells other than striated muscle

Trichinella spiralis



cells fail to induce Nurse cells, and either reenter the general circulation or die. Nurse cell formation results in an intimate and permanent association between the worm and its intracellular niche. At the cellular level, myofilaments and other related muscle cell components become replaced over a 14-16 day period by whorls of smooth membranes and clusters of dysfunctional mitochondria. The net result is that the host cell switches from an aerobic to an anaerobic metabolism.²³ Host cell nuclei enlarge and divide,²⁴ amplifying the host's genome within the Nurse cell cytoplasm.²⁵ The Nurse cell-parasite complex can live for as long as the host remains alive. Most do not, and are calcified within several months after forming. In order for the life cycle to continue, an infected host must die and be eaten by another mammal. Scavenging is a common behavior among most wild mammals, and this helps to ensure the maintenance of *T. spiralis* and its relatives in their respective host species.

Cellular and molecular pathogenesis

The enteral (intestinal) phase includes larval stages 1 through 4, and the immature and reproductive adult stages. In humans, this phase can last up to 3 weeks or more. Developing worms damage columnar epithelium, depositing shed cuticula there. Later in the infection, at the onset of production of newborns, local inflammation, consisting of infiltration by eosinophils, neutro-



Figure 21.5. Newborn larva of *T. spiralis*. 70 x 7 μ m.

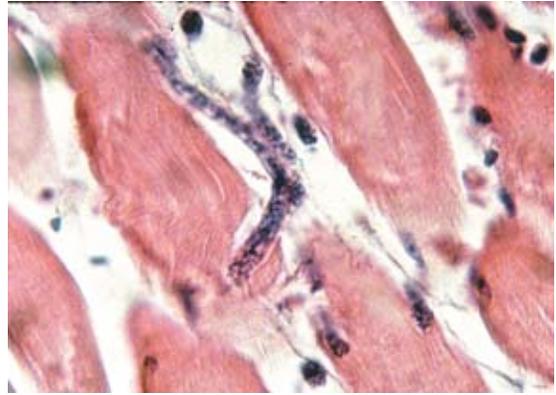


Figure 21.6. Newborn larva of *T. spiralis* entering muscle cell.

phils, and lymphocytes, intensifies in the local area. Villi flatten and become somewhat less absorbent, but not enough to result in malabsorption syndrome.

When larvae penetrate into the lymphatic circulation or bloodstream, a bacteremia due to enteric flora may result, and cases of death due to sepsis have been reported. Loss of wheat germ agglutinin receptors along the entire small intestine occurs.²⁶ The myenteric electric potential is interrupted during the enteral phase, and as the result, gut motility slows down.²⁶

The parenteral phase of infection induces most of the pathological consequences. It is dose dependent and is attributable directly to the migrating newborn larvae as they randomly penetrate cells (e.g., brain, liver, kidney, heart) in their search for striated skeletal muscle cells (Fig. 21.6). Cell death is the usual result of these events. The more penetration events there are, the more severe the resulting pathology. The result during heavy infection is a generalized edema. Proteinuria may ensue. Cardiomyopathies and central nervous system abnormalities are also common in those experiencing moderate to heavy infection.¹

Experimental infections in immunologically-defined strains of rodents have shown that the total number of muscle larvae produced was dependent upon numerous factors related to the immune capabilities of a given strain. Induction of interleukins 4, and 13,²⁷ as well as production of eosinophils and IgE antibodies,²⁸ appear to be essential for limiting production of newborn larvae and for the expulsion of adult worms. TNF-induced nitric oxide (NO) production is, however, not one of the effector mechanisms, since knockout mice unable to produce NO expelled their parasites in a normal fashion in the absence of local gut damage.²⁹ In NO+ mice, expulsion of adults was accompanied by cellular pathology surrounding the worms. Local production of nitric oxide during the development of inflammation may be a contributing factor to the development of intestinal

pathology during infection with trichinella. Whether or not these same mechanisms are invoked during infection in the human host is not known.

For an in depth look at the biology of *Trichinella spiralis*, see www.trichinella.org.

Clinical Disease

The clinical features of mild, moderate, and severe trichinellosis have been reviewed (Fig. 21.10).^{1, 30} The presentation of the disease varies over time, and, as a result, resembles a wide variety of clinical conditions. Trichinellosis is often misdiagnosed for that reason. The severity of disease is dose-dependent, making the diagnosis based solely on symptoms difficult, at best. In severe cases, death may ensue. There are signs and symptoms that should alert the physician to include trichinellosis into the differential diagnosis.

The first few days of the infection are characterized by gastroenteritis associated with diarrhea, abdominal pain, and vomiting. Enteritis ensues, and is secretory in nature. This phase is transitory, and abates within 10 days after ingestion of infected tissue. A history of eating raw or undercooked meats helps to rule in this parasitic infection. Others who also ate the same meats and are suffering similarly reinforces the suspi-



Figure 21. 7. An adult female *T. spiralis*, depicted *in situ*. Drawing by J. Karapelou.



Figure 21.8. Nurse cell-parasite complex of *T. spiralis*, *in situ*. Infected mouse was injected with India ink to visualize circulatory rete.



Figure 21.9. Nurse cell-parasite complex. Phase interference. Photo by E. Gravé.

cion of trichinellosis. Unfortunately, most clinicians opt for a food poisoning scenario at this juncture.

The parenteral phase begins approximately one week after infection and may last several weeks. Typically, the patient has fever and myalgia, bilateral periorbital edema, and petechial hemorrhages, which are seen most clearly in the subungual skin, but are also observable in the conjunctivae and mucous membranes. Muscle tenderness can be readily detected. Laboratory studies reveal a moderately elevated white blood cell count (12,000-15,000 cells/mm³), and a circulating eosinophilia ranging from 5% to as high as 50%.

Larvae penetrating tissues other than muscle gives rise to more serious sequelae. In many cases of moderate to severe infection, cardiovascular involvement may lead to myocarditis, but this aspect of the infection has been overrated as a clinical feature typical of most infections with this parasite, since most instances encountered by the clinician are of the mild variety.³¹ Electrocardiographic (ECG) changes can occur during this phase, even in the absence of symptoms. Parasite invasion of the diaphragm and the accessory muscles of respiration result in dyspnea. Neuro-trichinellosis oc-

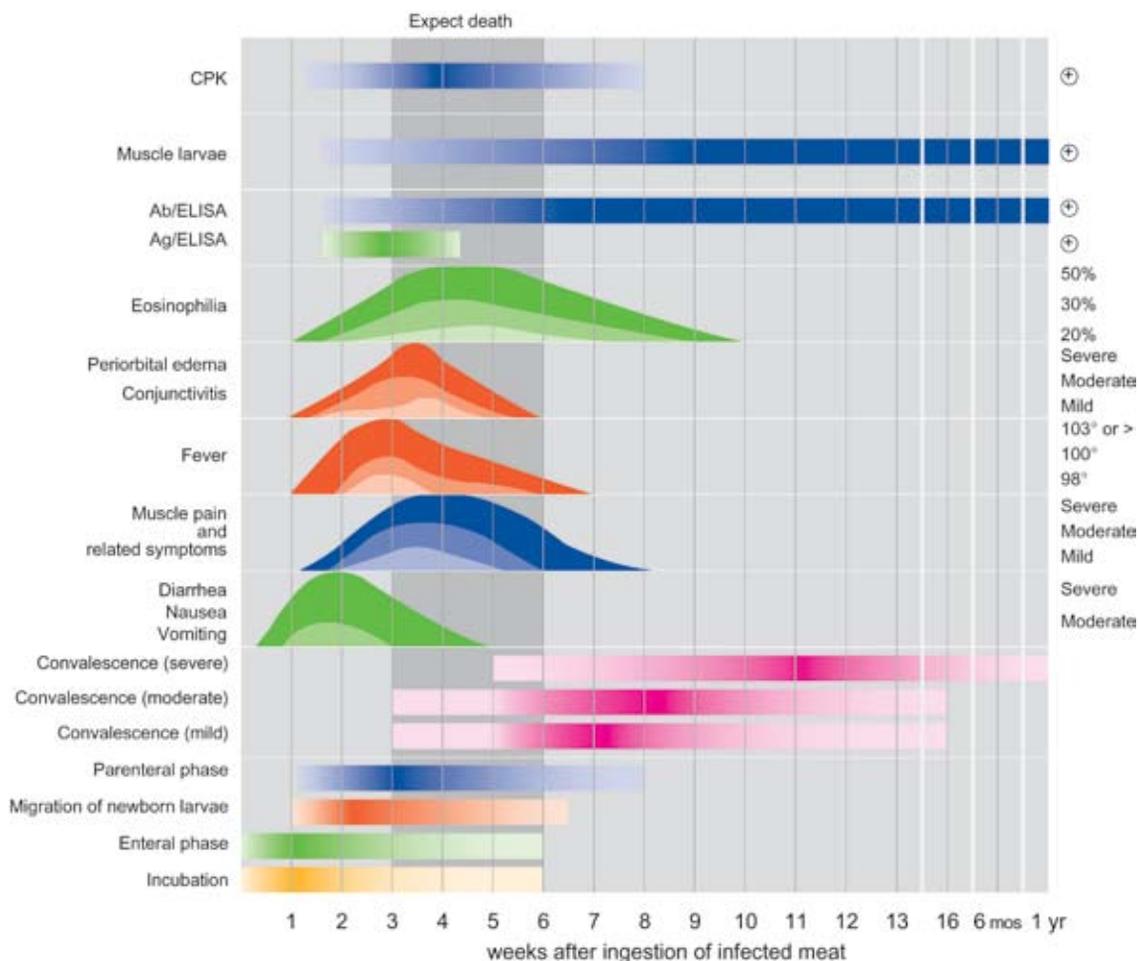


Figure 21.10. Summary of clinical correlations. The degree of manifestation of signs and symptoms is dependent upon the dose of larvae ingested. The stages of the parasite and the signs and symptoms associated with them are shown in the same colors.

curs in association with invasion of the central nervous system. Convalescent phase follows the acute phase, during which time many, but not all, Nurse cell-parasite complexes are destroyed.

Two clinical presentations have been described for *T. nativa* infections resulting from the ingestion of infected polar bear or walrus meat: a classic myopathic form, and a second form that presents as a persistent diarrheal illness. The second form is thought to represent a secondary infection in previously sensitized individuals.³²

Diagnosis

Definitive diagnosis depends upon finding the Nurse cell-parasite complex in muscle biopsy by microscopic examination (Fig 21.1), or detection of *Trichinella*-specific DNA by PCR.³³ PCR is very sensitive and specific for detecting small numbers of larvae in muscle tissue, but due to the infrequency of request

and the costs associated with maintaining such a capability, PCR is usually prohibitive for most hospital laboratories. This will undoubtedly change in the near future, as more and more parasitic infections become diagnosed routinely by PCR-based methods.

Muscle biopsy can be negative, even in the heaviest of infections, due to sampling errors. In addition, the larvae may be at an early stage of their development, making them inconspicuous, even to experienced pathologists. A rising, plateauing and falling level of circulating eosinophils throughout the infection period is not direct proof of infection, but armed with this information, the clinician could treat the patient as if the diagnosis of trichinella had been made. Bilateral periorbital edema, petechiae under the fingernails, and high fever, coupled with a history of eating raw or undercooked meats, is further indirect evidence for this infection. It is helpful to remember that wild mammals can also be sources of infection. Outbreaks of trichinellosis have been traced to hunters and the recipients of their kills.^{34, 35, 36}

Muscle enzymes, such as creatine phosphokinase (CPK) and lactic dehydrogenase (LDH), are released into the circulation causing an increase in their serum levels. Serological tests begin to show positive results within two weeks. ELISA can detect antibodies in some patients as early as 12 days after infection.³⁷

Treatment

There is no specific anthelmintic therapy, even after a definitive diagnosis is made. Mebendazole given early during the infection may help reduce the number of larvae that might lead to further clinical complications, but the likelihood of making the diagnosis in time to do so is remote. Anti-inflammatory corticosteroids, particularly prednisolone, are recommended if the diagnosis is secure.^{1, 29} Rapidly destroying larvae with anthelmintics without use of steroids may actually exacerbate host inflammatory responses and worsen disease (e.g., Jarisch-Herxheimer reaction). The myopathic phase is treated in conjunction with antipyretics and analgesics (aspirin, acetaminophen), and should be continued until the fever and allergic signs recede. Because of their immunosuppressive potential, steroids should be administered with caution.

Prevention and control

Within the last 10 years, outbreaks of trichinellosis in the United States have been rare and sporadic in nature.³⁸ Most have been associated with the ingestion of raw or undercooked meats from game animals and not from commercial sources. This represents a shift in the epidemiology of outbreaks compared to 20-30 years ago, when commercial pork sources of infection were much more common than today. Pigs raised on individual farms, as compared to commercial farm operations, are more likely to be fed uncooked garbage,

and thus acquire the infection. This is because feeding unprocessed garbage containing meat scraps is against federally mandated regulations. In the past 10 years, small farms have, in the main, been bought up and replaced with larger so-called “factory” farms, in which upwards of 10,000 pigs can be managed with a minimum of labor. Enforcement of laws governing the running of large production facilities is a full time activity and has been key in reducing the spread of diseases infecting livestock and humans alike.³⁸

As already mentioned, top carnivores such as bear, fox, cougar, and the like often become infected. Hunters sharing their kill with others are best warned to cook all meat thoroughly. Herbivores can harbor the infection as well, since most plant eaters occasionally ingest meat when the opportunity arises. Epidemics due to eating raw horsemeat have been reported from France, Italy, and Poland.³⁹

Meat inspection is nonexistent in the United States with respect to trichinella. In Europe, the countries participating in the common market employ several strategies for examining meat for muscle larvae. Most serve to identify pools of meat samples from given regions. If they are consistently negative, then a trichinella-free designation is applied to that supply of meat. Nonetheless, rare outbreaks occur, despite this rigorous system of inspection.

Trichinellosis due to *Trichinella spiralis* can be prevented by either cooking meat thoroughly at 58.5° C for 10 minutes or by freezing it at -20° C for three days. However, with other species of trichinella, the story is quite different, since they are mostly found in wild animals. For example, bears and raccoons have special proteins in their muscle cells that prevent ice crystals from forming during periods of hibernation, inadvertently permitting survival of the larvae at temperatures below freezing.⁴⁰ Hence, the only way to render those meats edible is to cook them thoroughly.

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