21. Trichinella spiralis
(Railliet 1896)

Introduction

Trichinella spp. are unusual nematodes compared to most in that they live their lives as intracellular parasites. All members of this genus are in the Order Trichurida. Thus, they are distantly related to Trichuris trichiura and Capillaria spp. The genus Trichinella has undergone much revision over the last few years, due largely to the advent of reliable DNA probes and their use in the polymerase chain reaction (PCR). There are nine genotypes recognized for this complex as determined by PCR. The diseases they cause are collectively referred to as trichinellosis. The most prevalent human infections are caused by Trichinella spiralis, followed by T. nativa and T. britovi. Currently, prevalence is low within the United States, appearing only as scattered outbreaks.

Domestic pigs are the dominant reservoir host for T. spiralis. Its prevalence is significantly higher in parts of Europe, Asia and Southeast Asia than in the United States. It is now considered endemic in Japan and China. No infections of any species have been reported from Puerto Rico or mainland Australia.

A recent outbreak of T. pseudospiralis in Thailand has been reported. A new species, Trichinella paupae, which is probably related to T. pseudospiralis, has been described in sylvatic and domestic pigs in Papua New Guinea.

Trichinella spp. infect nearly all orders of mammals, making it one of the world’s most widely-distributed parasite groups. The major reservoir hosts for T. nativa are polar bears and walruses. T. britovi is another sylvatic form of trichinellosis, being found throughout most of Asia and Europe in numerous carnivorous animal species (e.g., fox, opossum, dog, cat). T. nelsoni infection occurs in Equatorial Africa and utilizes hyenas and large cats as reservoir hosts. Most animals acquire trichinellosis by scavenging.

Historical Information

Owen, in 1835, was first to formally describe the larva. He observed the larva under the microscope in a piece of infected diaphragm muscle tissue obtained from a 51-year-old bricklayer who died of tuberculosis. Paget, then a first year medical student, obtained a piece of the same diaphragm while watching the autopsy, and also saw the worms using a borrowed microscope at the British Museum. By 1860, the main features of the life cycle of T. spiralis were reported by Virchow and Leuckart.

The first clinical case of trichinellosis was described by Friedrich in 1862, and the first fatality was reported by Zenker in 1860. For an excellent summary of the history of trichinellosis, see Campbell.

Life Cycle

Infection begins by ingesting raw or undercooked meats containing the Nurse cell-larva complex (Fig. 21.1). The precocious infective larvae (first-stage worms) are released by the action of digestive enzymes in the stomach, and locate to the upper two...
thirds of the small intestine. The outer, impervious cuticular layer (epicuticle) is altered by alkaline conditions and pancreatic digestive enzymes, allowing the freed worms to receive environmental cues that help them discern their location within the host. The immature parasites are stimulated to penetrate the columnar epithelium at the base of the villus. They live within a row of these cells, and are thus considered intra-multicellular organisms (Fig. 21.2).

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

Patency begins five days after mating. Adult females produce live offspring, referred to as newborn larvae (Fig. 21.5), measuring 0.08 mm long and 7 µm in diameter. The female continues producing newborns as long as host immunity does not develop, which interferes with the process.

The newborn larva possesses an anterior stylet located in its oral cavity, which it uses to penetrate cells. Larvae enter the lamina propria, then penetrate into either the mesenteric lymphatics or into the bloodstream. Most larvae eventually find their way into the general circulation, and are then distributed throughout the body.

Migratory newborns emerge from the capillaries and enter cells. There appears to be no tropism for any particular cell type. They either remain in or leave that cell, depending upon the environmental cues received. Most cell types in the body die as the result of invasion by larvae; skeletal muscle fibers are the one notable exception (Fig. 21.6). Not only do they remain alive after parasite invasion, they also support further growth and development of the larvae. This process is termed Nurse cell formation and takes about 20 days to complete. However, larval development within the Nurse cell is precocious. Larvae 14 days old or older are now infectious for the next host.

Larvae that have penetrated tissues other than striated muscle cells fail to induce Nurse cell formation, and either reenter the capillaries or become surrounded by granulomas and eventually die.

The enteral phase of the infection in the small intestine can last 2-3 weeks, but eventually the adult worms are expelled by the acquisition of immunity, most likely mediated by IgE and eosinophils.

Cellular and Molecular Pathogenesis

Enteral Phase

The enteral (intestinal) phase includes larval stages 1 through 4, and the immature and repro-
Trichinella spiralis

Larvae are ingested in raw or undercooked meats
Larvae are released from Nurse cells in stomach
Larvae enter small intestine
Adults mature and live in small intestine
Larva matures in muscle
Newborn larvae are carried throughout bloodstream
Newborn larva enters skeletal muscle cell
Female sheds newborn larvae that enter lymph or blood

Normal (red) and calcified Nurse cell-larvae complexes

PATHOLOGY
Heart failure
CNS damage

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ductive adult stages. During the several-week-long period of the enteral infection, the intestinal epithelium becomes compromised at the local level and beyond. The developing larval stages damage the columnar epithelium, depositing their shed cuticula there. Enteritis ensues, and is secretory in nature. Later in the infection, as worms shed newborns, local inflammation consisting of infiltration by eosinophils, neutrophils, and lymphocytes is intensified.

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 without recovery of them. The myenteric electric potential is affected during the enteral phase, and gut motility slows down.

In experimental infections in immunologically-defined strains of rodents, the number of larvae produced was dependent upon numerous factors related to the immune capabilities of a given strain. Interleukins 4 and 9, as well as production of eosinophils and IgE antibodies appear to be essential factors and effector mechanisms for expulsion of adult worms. However, whether or not these same events occur in human infections to limit infection is not known.

Parenteral Phase

The most interesting feature of the parenteral phase is the formation of an association between the parasite and the host (i.e. the Nurse cell-parasite complex, - Figure 21.8.) that can last essentially for the life of that host, regardless of the species. Nurse cell formation has been studied in synchronously infected mice. This complex is characterized by a remarkable series of host cellular and molecular rearrangements.

Myofilaments and other related muscle cell structures are replaced over a 14-16 day period with smooth membranes and clusters of dysfunctional mitochondria. Nuclei enlarge and divide, thus amplifying the host's genome within the Nurse cell cytoplasm. Over-expression of collagen type IV and type VI mRNAs results in the production of a thick outer acellular capsule. Angiogenesis rapidly ensues, initiated by VEGF synthesis, beginning on day 7 after the larva enters the muscle cell. A circulatory rete is the result (Figure 21.9.), which most likely functions to allow the worm inside to obtain nutrients and dispose of its wastes.

Nurse cell formation is most likely induced by the secretions of the developing parasite, and emanates from the stichosome. The stichosome consists of a row of discoid cells, each of which contains secretory granules of a single morphological type. There are at least five distinct stichocyte cell types comprising the stichosome. Many different proteins are secreted into the Nurse cell-parasite complex during Nurse cell formation. Some of them enter the host cell nuclei and remain there throughout the infection. Speculation favors a transcriptional role for these unusual tyvelosylated secreted proteins. However, none have been characterized in terms of their potential role(s) in Nurse cell formation.

As larvae penetrate cells, they can cause extensive damage, depending on the tissue in question. This situation is most problematic to the host when it involves the heart and central nervous system.
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Myocarditis is typical in heavy infections. Nurse cells cannot form in heart muscle cells; thus, myocarditis is transitory. In the central nervous system, newborn larvae tend to wander before leaving the tissue. Much of the inflammation in the brain is initiated by petechial hemorrhages.

After parasites enter skeletal muscle fibers, they induce a progressive infiltration by the inflammatory cells. Edema and myositis develop about 14 days after the penetration of muscle fibers. It is likely that this is due to exposure to tyvelosylated secreted proteins, which are highly antigenic.

The extent of infection is primarily related to the number of larvae that enter muscle, but there is considerable variation in clinical presentation depending on the species and type of muscle. For instance, some humans invaded with 15 T. spiralis larvae per gram of diaphragmatic muscle have died as the result, while others have survived this dose.

Many, but not all, Nurse cell-parasite complexes become calcified and die within months after forming. In many cases, viable infective larvae can be recovered for some time after the death of the host. In the laboratory, infected mouse muscle tissue kept at 4°C harbored live larvae up to six months after the animal was sacrificed. This has enormous selective advantage regarding its ability to distribute itself throughout the environment, since most dead carcasses are scavenged by a wide variety of mammals.

Clinical Disease

The clinical features of mild, moderate, and severe trichinellosis are depicted in Figure 21.10. Clinical aspects of trichinellosis are summarized by Murrell and Bruschi² and Capo and Despommier.³

Trichinellosis resembles a wide variety of clinical conditions, and is often misdiagnosed for that reason. The severity of clinical trichinellosis is dose-dependent, making the diagnosis based solely on symptoms difficult at best. However, there are clues, even in the early stages of the disease, which 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. This phase is very 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 suspicion of trichinellosis. Unfortunately, most clinicians opt for a food poisoning scenario at
this juncture in the infection.

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 observed 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/mm$^3$), and a circulating eosinophilia ranging from 5% to 50%.

Larvae penetrating tissues other than muscle gives rise to more serious sequelae. In many cases of moderate to severe infection, cardiovascular involvement leads to myocarditis. Electro-cardiographic (ECG) changes are frequently noted during this phase. Parasite invasion of the diaphragm and the accessory muscles of respiration results in dyspnea. Neurotrichinellosis also occurs in association with central nervous system invasion. Convalescent phase follows the acute phase, during which time many 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.

**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.

**Diagnosis**

Definitive diagnosis depends upon finding the Nurse cell-parasite complex in muscle biopsy by microscopic examination (Figure 21.1; Figure D.49, Appendix D), or detection of Trichinella-specific DNA by PCR. 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 the best-trained pathologist. A rising, plateauing and falling level of circulating eosinophils throughout the infection period is not direct proof of infection, but with this information in hand, the clinician could treat 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, further solidifies the 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.

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.

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. 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 continued until the fever and allergic signs recede. Because of their immuno-suppressive potential, steroids should be administered with caution.

Prevention and Control

Trichinellois 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, certain wild animals, such as bears and raccoons, have substances in their muscles that prevent ice crystals from forming during their hibernation, inadvertently permitting survival of the larvae. Hence, their flesh must be cooked thoroughly to destroy the larvae.

In the United States, most (90-95%) infections with T. spiralis can be traced back to a single episode of eating undercooked or raw pork purchased from commercial sources (e.g., sausage). In addition, some outbreaks have been traced to ground beef adulterated with pork scraps. Finally, sporadic epidemics were caused by ingestion of undercooked meat of bears, cougars and other wild animals.

In the USA, tracing a sample of contaminated pork that was sold commercially back to its farm source is often futile. This is because the origin of individual pigs is not identifiable after the animals are sold at auctions. People raising pigs for their own private consumption are not subjected to the same regulations as farmers who run large-scale factory pig farms. Hence, meat scraps and wild rodents often enter the digestive tract of solitary animals that are raised more as an afterthought than for food. For this reason, alone, trichinellois will always present as sporadic epidemics.

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