Brief Overview about Trichinellosis; Epidemiology, Pathogenesis, and Clinical Manifestations

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Abstract
Background
Trichinellosis is a worldwide food-borne parasitic disease. Pork and its products are the main sources of infection. Trichinella has a wide range of hosts including humans and can infect more than 150 species of animals. In Egypt, T. spiralis may be found in fresh and processed pork. However, domestic trichinellosis is present in Egypt, Few reports of *T.spiralis* infection in fresh and processed pork in Egypt are available. In 1975 outbreak of human trichinosis was documented in French visitors. After that the prevalence rate decreased to 1.7% in 1995–1999. Infection is initiated by ingesting raw or undercooked meat harboring the nurse cell-larva complex. Larvae release from muscle tissue then locate to the upper two-thirds of the small intestine. The immature parasites penetrate the columnar epithelium at the base of the villus. The course of the disease can be abortive, mild, moderate or severe depending on species of Trichinella, the infective dose and phase of infection. The most pathogenic species is *T.spiralis*. Principally, infection in the man can be divided into two phases: an intestinal phase and a muscular phase. Intestinal (enteral) phase is caused by larvae developing in the small intestine immediately after the onset of infection. Muscular phase is caused by NBL delivered by females and transported via lymphatic and blood vessels into the muscles, where larvae capsulate and survive for months or years.
Keywords: Trichinellosis

INTRODUCTION

Trichinellosis is a worldwide food-borne parasitic disease. Pork and its products are the main sources of infection. *Trichinella* has a wide range of hosts including humans and can infect more than 150 species of animals . The International Commission on Trichinellosis (ICT) reported a total of about 65818 cases of human trichinellosis from 1986 to 2009 and 42 deaths reported from 41 countries **(1)**.

In 2014, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) composed a list of 24 parasites ranked according to nine global criteria, *Trichinella spiralis* ranked the first in international trade. They also published a list of the top ten food-borne parasites that affect the health of millions of people every year worldwide causing serious health problems and *T.spiralis* occupied the seventh place **(2).**

Trichinosis less commonly occurs in the tropics. Worldwide about 10,000 trichinosis infections occur a year. At least 55 countries including the United States, China, Argentina, and Russia have had been reported cases. Trichinosis rates in USA decreased from 400 cases/year in 1940s to 20 or fewer /year in 2000s **(3).**

Trichinellosis outbreaks have been reported in 55 countries with an annual global average of 5751 cases and five deaths. It is estimated that the global number of disability adjusted life years (DALYs) due to trichinellosis be 76 per billion persons per year **(4).**

From 2004 to 2009 in China, 15 outbreaks of human trichinellosis affected 1387 people and caused 4 deaths. Pork is the predominant source of outbreaks of human trichinellosis in China. Out of 15 outbreaks, 12 (85.71%) were caused by eating raw or undercooked pork**.** Trichinellosis has become an emerging and re-emerging zoonotic disease with health, social, and economic impacts in developing countries **(5).**

Among domestic animals, interestingly, it has been reported that mutton, the meat of adult sheep, is the second most common food that causes trichinellosis in China, responsible for at least 23 outbreaks**.** Moreover, consumption of beef meat has been reported as source of human infection in China**.** While the source of a natural route of infection of sheep or beef cattle is unclear, experimental studies have shown that sheep, goats and cattle could be infected with *Trichinella* spp. **(5).**

During the period of 2000 to 2012, beef meat was reported to be the cause of infection in four patients in the U.S.A. Beef or other herbivorous animal meat may be mixed with infected meat from other sources and sold in restaurants and stores. For example, *Trichinella* infected pork meat mixed with beef was the source of a large outbreak of trichinellosis in Turkey affecting 1098 people **(6).**

In Turkey, three outbreaks of trichinellosis occurred from the consumption of pork in Antalya (more than 40 people), Bursa (seven people) and Izmir (more than 600 people) between 2003 and 2004. In countries where most of the population follows the Muslim or Judaism religious law, the consumption of pork and the meat of carnivores is forbidden, therefore, *Trichinella* species infection is seldom documented in humans. However, the increasing secularism, demographic changes and the presence of populations with different religions in these countries along with the increasing tourism lead to increase in pig production, and the consumption of game meat **(7).**

In Egypt, *T. spiralis* may be found in fresh and processed pork. However, domestic trichinellosis is present in Egypt, Few reports of *T.spiralis* infection in fresh and processed pork in Egypt are available. In 1975 outbreak of human trichinosis was documented in French visitors. After that the prevalence rate decreased to 1.7% in 1995–1999 **(8)**.

Trichinellosis has been detected in rats, domestic pigs and stray dogs from Alexandria with prevalence 13.3% **(8).** The prevalence of *T.spiralis* larvae infection in slaughtered pigs in Albasatin slaughterhouse, Cairo Governorate, Egypt was1.08%**.** In Upper Egypt the infection rate of *T.spiralis* is 5% & 2% in Assiut and Sohage Governorates, respectively. The low prevalence rate of infection with trichinellosis in pigs might be related to hygienic conditions for rearing pigs in private farms or large farm and raising of the Egyptian pigs is mainly indoors away from the sources of infection **(9).**

The enteral phase:

Infection is initiated by ingesting raw or undercooked meat harboring the nurse cell-larva complex. Larvae release from muscle tissue then locate to the upper two-thirds of the small intestine. The immature parasites penetrate the columnar epithelium at the base of the villus. They live within a row of these columnar epithelial cells and are considered intramulti-cellular organisms. Larvae moult four times and develop into adults. After mating the new born larvae migrate through the blood stream to voluntary controlled muscles where they encyst **(10).**

The adult stage that inhabits the epithelial layer of the small intestine of the host induces an acute immune-mediated inflammatory response reflected in structural, cellular and physiological changes**.** These changes are associated with marked changes in epithelial cells, increasing in numbers of inflammatory cell types and release of inflammatory mediators **(11).**

Light infection causes little damage. However, severe infection may cause hyperemia, petechiae of the serosa, excessive mucous secretion, enlarged Peyer's patches and dilatation of loops of bowel. Histopathology of the small intestine reveals that there is intense inflammatory response with mixed cellular infiltration mainly neutrophils, eosinophils and lymphocytes in the jejunum **(11).**

T.spiralis also may cause trophic changes in both circular and longitudinal smooth muscle layers of both jejunum and ileum with marked villous atrophy and crypt hyperplasia. These are associated with marked changes in epithelial cells and increase in inflammatory cell types and mediators **(11).**

Migratory phase:

In migratory phase the pathology is caused by the larvae released into the intestinal mucosa, which subsequently migrate to the blood vessels. They spread throughout the body until reaching the striated skeletal muscles. Migrating *Trichinella* larvae and their metabolites stimulate an immediate reaction that causes immunological, pathological, metabolic disturbances and the various clinical phenomena observed during the acute stage of the infection **(12).**

Muscular phase:

After invasion of skeletal muscles larvae induce a significant series of cell physiological changes. These changes cause transformation of the fully differentiated muscle cell to transform into nurse cell that supports the growth and development of the larva. This phase is associated with inflammatory and allergic responses caused by the invasion of the muscles by the migrating larvae **(13).**

This invasion can damage the muscle cells directly or indirectly stimulating the infiltration of inflammatory cells, primarily eosinophils. A correlation between the eosinophil levels and serum muscle enzymes has been observed in trichinellosis patients, suggesting that muscle damage may be mediated by these granulocytes**.**Thus, progressive eosinophilia is the most relevant clinical finding of the muscular phase of Trichinellosis**.**The invasion of the diaphragm and accessory muscles of respiration by the parasite results in dyspnea **(13).**

Neurological Involvement:

Either gray or white matter of the brain, cerebellum, pons, or spinal cord may be involved in neurotrichinellosis. Central nervous system damage is caused either directly by the parasitic larvae or indirectly by immune mediated pathogenesis, reaction to toxins, vascular damage and tumor necrosis factor (TNF) which in turn leads to eosinophil toxicity**.** Peripheral nerves are less frequently affected **(12).** *Trichinella* larvae can migrate in central nervous system (CNS) and cause diffuse lesions, obstruction of the blood vessels, and inflammatory infiltrate. The larval and muscle breakdown products may mediate different pathologic alterations **(14).**

The larvae either produce pathologic manifestations in tissues before returning into the circulation or may be trapped and consequently destroyed, causing inflammatory reactions**.** Microscopic nodules, consisting of clear necrotic areas that surround the parasites, may be detected in the subcortical white matter. *Trichinella* larvae may also present in cerebrospinal fluid (CSF) or meninges. Edema, hyperemia, and punctuate hemorrhages occur most commonly in the brain substance**.** Nodules of glial cells and small hemorrhages develop in the periventricular and other regions of the white matter **(12).** Vascular alterations surrounding the larvae are considered the main mechanisms that lead to neurological damage **(15).**

Cardiac Involvement:

The process of encystment and nurse cell formation is unique to skeletal muscle and does not

take place within the heart**.** *T.spiralis*-associated myocarditis is not caused by the direct larval invasion of the myocardium with encystation but is likely induced by an eosinophil-enriched inflammatory response resulting in eosinophilic myocarditis similar to the pathogenic process associated with tropical endomyocardial fibrosis**.** Some patients with trichinellosis develop organ-specific autoantibodies, whose role in pathogenesis remains unclear **(16).**

Hepatic involvement:

Liver involvement were noticed either during or after the intestinal phase of trichinellosis**.** The damage can be caused by larval injuries directly or indirectly through eosinophils and immunologic reactions. Significant injuries may occur in the liver in severe infections. Some of them were due to the toxic and allergic mechanisms. In these cases, liver frequently enlarged due to dystrophic lesions such as fatty degeneration **(17).**

Hypoproteinemia commonly occurs and may be explained by the hepatocellular dysfunction, allergic capillaropathy that induced by eosinophils and deficitary digestion and absorption of the proteins consequent to the alterations of the intestinal mucosa **(17).** Total protein decrease is based on the decrease of the albumin fraction (hypoalbuminemia). Moreover, increase of the globulin fraction leads to a significant decrease albumin and globulin (A/G) ratio **(17).**

Renal involvement:

It Was emphasized that hypercoagulability status may lead to glomerular deposition of fibrin in trichinellosis. Dystrophic lesions (sometimes lipid-related) and tubuloglomerular alterations may explain the progression to acute glomerulonephritis with signs of renal failure **(17).** The various types of modifications were attributed to intensive parasitic invasion, substantial release of antigens, tissue destruction, increased catabolism, or hypovolemia **(12).**

Nevertheless, it seems that the mechanism responsible for the development of renal lesions is based upon toxic and allergic manifestations **(17).** Increased level of immunoglobulin E especially between the third and fourth weeks of illness is evidence that supports the allergic status of trichinellosis. Also, development of the eosinophilic capillaropathy and symptoms such as urticaria or periorbital angioedema supports the allergic status **(12).**

Cloudy swelling and obvious opacity may be found in the renal cortex. The renal parenchyma may be normal in consistency with fatty degeneration. The location of the swelling may be intracapsular, intratubular and interstitial. Focal hemorrhages and infarctions may be observed. These changes were caused by direct invasion of renal tissue by larvae, deposition of immune complexes or due to the significant increase in plasma urea nitrogen. This increase may be due to impaired regulation of renal tubular urea transport or due to increased skeletal muscle breakdown **(18)**.

Clinical manifestations

The course of the disease can be abortive, mild, moderate or severe depending on species of *Trichinella*, the infective dose and phase of infection. The most pathogenic species is *T.spiralis*. The clinical signs appear after the ingestion of 100–300 infective larvae and consumption of 1000–3000 larvae can cause severe trichinellosis. Principally, infection in the man can be divided into two phases: an intestinal phase and a muscular phase. Intestinal (enteral) phase is caused by larvae developing in the small intestine immediately after the onset of infection. Muscular phase is caused by NBL delivered by females and transported via lymphatic and blood vessels into the muscles, where larvae capsulate and survive for months or years **(19).**

Natural History:

Trichinosis is a self-limiting infection lasting in light infections 2–3 weeks and in heavy ones at

the most 2–3 months. Except in heavy infections mortality is low. Light infections are often asymptomatic and routine examinations of diaphragms at autopsy have shown a significant number of calcified cysts in endemic areas **(19).**

Incubation Period:

From eating infected meat, the development of symptoms during the enteric phase is up to 7 days after infection, and for the migratory phase from 7 to 21 days **(19).**

Symptoms and Signs:

The symptomatology depends on the level of infection and can be related to the number of larvae per gram of muscle. Light infections (subclinical) up to 10 larvae, moderate 50–500 larvae and severe and possibly fatal infections more than 1000. In symptomatic cases symptoms develop in three stages: enteric (invasion of the intestine) phase, migration of the larvae (invasive phase) and a period of encystation in the muscles **(19).**

Enteric Phase:

Irritation and inflammation of the duodenum and jejunum where the larvae penetrate cause nausea, vomiting, colic and sweating. It is resembling an attack of acute food poisoning. There may be a maculopapular skin rash and in one-third of cases symptoms of pneumonitis occur between the 2nd and 6th days, lasting about 5 days **(19).** Intestinal signs are diarrhea (loose stools to as many as 10 to 15 stools per day, frequently containing mucus but free of blood) and abdominal pain. These signs and symptoms usually precede fever and myalgia by three to four days. They disappear in less than one week. It has been observed that the shorter the duration between infection and the appearance of diarrhea and fever, the longer the duration of both fever and facial oedema **(20).**

Migratory (Invasion) Phase:

The cardinal symptoms and signs of this phase are severe myalgia, periorbital oedema and eosinophilia. Myalgia affects various muscle groups, and its intensity is related to the severity of the disease. It most frequently affects the muscles of the cervix, trunk, and upper and lower extremities. It may also affect the masseters. The pain usually appears upon exertion, although most persons with severe trichinellosis or phlebitis associated with trichinellosis also experience myalgia at rest **(19).**

Some persons with severe disease become disabled with a profound muscle weakness as a result of pronounced angiomyositis-type lesions and neuro-muscular disturbances. The restriction of movement due to the pain associated with exertion leads to contractures of the upper and lower limbs, nuchal pseudorigidity, and occasionally trismus. Severe myalgia generally lasts for two to three weeks. There is difficulty in mastication, breathing and swallowing due to the involvement of the muscles and there may be some muscular paralysis of the extremities **(20).**

Periorbital and facial oedema are very typical signs of trichinellosis, although their intensity varies depending upon the intensity of the reaction to the infection. In the severe form of trichinellosis, oedema is symmetrical and extends to the upper and lower extremities. There is a high remittent fever with typhoidal symptoms. Fever is one of the earliest and most common signs of trichinellosis. Body temperature increases rapidly, usually stabilizing at 39°C to 40°C. The fever usually lasts from 8 to 10 days, although it can persist for up to three weeks when the disease is severe **(19).**

Splinter haemorrhages under the nails, conjunctival and subungual haemorrhagic lesions are caused by vasculitis which is the leading pathological process of trichinellosis. In addition, maculo-papular rash occurs after the onset of muscular pain **(19).**

Characteristically, there is a hypereosinophilia from the 14th day which decreases after a week and persists at a lower level. An absence of eosinophilia denotes a poor prognosis. The lymph glands may be enlarged as well as the parotid and submental glands. Occasionally, there is splenomegaly. In severe cases, there may be subpleural, gastric and intestinal haemorrhages **(20).**

Encystment Phase:

This is the third stage and may be severe. There may be cachexia, oedema and extreme dehydration. During the 2nd month after infection there is a decrease in muscle tenderness, fever, itching subsides and congestive heart failure may appear. Damage to the brain may persist with neurological signs which may clear up later or persist. Gram-negative septicaemia from organisms introduced by the larvae, permanent hemiplegia and Jacksonian epilepsy 10 years after an attack of trichinosis, have been described **(20).**

Complications

Complications of trichinosis in adults versus children demonstrated that trichinosis is a more serious disease in children. Children suffered complications more frequently than adults even if the severity of disease had been mild or moderate. Children surpassed adults in neuropsychiatric complications. A severe asthenia with a diminution in school performance was recorded in many infected school children. Many children complain of sight ailments, diminution of visual acuity, nistagmus and complications of the cardiovascular system. Adult females were more susceptible to complications, perhaps resulting from higher initial consumption of muscle larvae through women's habit of tasting meat preparations that have not yet been thermally processed **(21).**

Comparison of immediate complications revealed their higher prevalence in urban patients versus rural patients a fact which might be explained by increased resistance of the inhabitants of rural areas to infection with trichinosis due to repeated exposure to *T.spirallis* larvae caused by regular consumption of pork meat from their own household. Urban consumers typically prefer consumption of pork meat from commercial sources. However, cardio-vascular and ophthalmological complications were more frequent in the rural patients as compared to urban patients **(22).**

Neurological complications

Neurotrichinellosis represents one of the most important complications in the course of severe trichinellosis which sometimes may be fatal. It occurs in 10% to 24% of cases **(20).** Patients with severe disease can show consciousness disorders or excessive excitement and apathy. Sometimes they have meningitis or encephalopathy. Dizziness, nausea, and tinnitus are transient. Facial nerve paresis and Babinski's sign have also been observed in severe cases **(23).**

Brain damage that usually observed within a few days after the onset of fever can result in diffuse encephalopathy or focal signs such as disorientation, memory disturbances, frontal syndrome, behavioral disturbances, transient hemiparesis, oculomotor dysfunction, aphasia, and cerebellar syndrome. Neuromuscular disturbances decreased muscular strength and tendon reflexes, dysphagia, and trismus usually occur at the beginning of the disease and may persist for a long period of time **(23).**

Ocular complications

Ocular lesions appear during the acute stage of the disease and result from disturbances in microcirculation. The typical characters are edema and vascular lesions within the conjunctiva, the uvea, the retina, and the optic nerve. Retinal lesions are rarely induced by migrating

T.spiralis larvae which penetrate ciliary arterioles and the central artery of the retina leading to irreversible damage to eyesight. An intense invasion of muscles of the ocular bulb provokes pain when moving the eyeballs, muscle paralysis, diplopia or a disturbed accommodation. The ophthalmologist is often the first contact because of the swollen eyelids and conjunctivitis and the suspect may arise from clinical history of ingesting raw or inadequately cooked meat **(24)**

Cardiovascular complications

Trichinellosis with cardiovascular complications is occurring in 10% to 60% of all patients. Most of the myocardial damage occurs during the invasive infective stage**.** The above-mentioned cardiovascular complications include myocarditis, thromboembolism, pericarditis, and Takotsubo cardiomyopathy. These cardiovascular problems can occur in moderate-to-severe cases of trichinellosis, usually later in the infection. Among them, myocarditis develops in 5% to 20% of all the infected patients **(20).** It is not only the myocardial changes in trichinosis that are responsible for the cardiovascular complications, but also arrhythmias caused by hypokalemia, adrenal gland insufficiency, and functional changes in the blood vessel circulation. Important clinical manifestations that should prompt cardiovascular investigation include chest pain, dyspnea, palpitation, edema, cutaneous petechiae and new onset heart murmurs **(24)**

Respiratory complications:

Respiratory complications are less frequent. They may happen during both the early and late stages of the disease. Dyspnea is relatively common and is caused mainly due to parasite invasion and subsequent inflammation of respiratory muscles such as the diaphragm. The complications include pneumonia, obstructive bronchitis, Loffler-type infiltrates, ventilation failure and bacterial pleurisy **(25)**.

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