REVIEW

New aspects of human trichinellosis: the impact of new *Trichinella* species

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Trichinellosis is a re-emerging zoonosis and more clinical awareness is needed. In particular, the description of new *Trichinella* species such as *T papuae* and *T murrelli* and the occurrence of human cases caused by *T pseudospiralis*, until very recently thought to occur only in animals, requires changes in our handling of clinical trichinellosis, because existing knowledge is based mostly on cases due to classical *T spiralis* infection. The aim of the present review is to integrate the experiences derived from different outbreaks around the world, caused by different *Trichinella* species, in order to provide a more comprehensive approach to diagnosis and treatment.

on anti-inflammatory drugs and antihelminthics such as mebendazole and albendazole; the use of these drugs is now aided by greater clinical experience with trichinellosis associated with the increased number of outbreaks.

The description of new *Trichinella* species, such as *T murrelli* and *T papuae*, as well as the occurrence of outbreaks caused by species not previously recognised as infective for humans, such as *T pseudospiralis*, now render the clinical picture of trichinellosis potentially more complicated. Clinicians and particularly infectious disease specialists should consider the issues discussed in this review when making a diagnosis and choosing treatment.

SYSTEMATICS

Trichinellosis results from infection by a parasitic nematode belonging to the genus trichinella. Trichinellosis has been an important, though often unrecognised, disease for thousands of years. Species of trichinella responsible for the infection are widely distributed, including the Arctic, temperate lands, and the tropics. Virtually all mammals are susceptible to infection by one or more species; however, humans appear to be especially prone to developing clinical disease. Infection with wild animal species of trichinella is far more common than is generally recognised.¹ Human trichinellosis is an important food borne zoonosis because of its epizootic nature and the economic burden associated with preventing its incursion into the human food chain. Its importance in even developed countries is exemplified by the fact that over 20 000 cases have occurred in Europe from 1991–2000.¹

From the time of the discovery of trichinella in 1835 until the middle of the next century, it was commonly assumed that all trichinellosis was caused by a single species, *Trichinella spiralis* (Owen, 1835). More than a century later, *T spiralis* had been reported from more than 100 different naturally or experimentally infected mammalian hosts and was believed to be a single species with low host specificity and spread around the world with the movement of domestic swine. Over the last decade, the application of molecular and biochemical methods in conjunction with experimental studies on biology have resulted in the identification of seven *Trichinella* species, which

Trichinellosis is a parasitic infection caused by a nematode belonging to the genus trichinella. Virtually all mammals are susceptible to infection by one or more species of the genus; however, humans appear to be especially prone to developing clinical disease. Over the past decade, the number of outbreaks around the world appear to have increased markedly, reflecting a changing epidemiological paradigm. The severity of the clinical course depends on parasitic factors such as the species involved, the number of living larvae ingested, and host factors such as sex, age, ethnic group, and immune status. It is the purpose of this review to highlight the changes in our understanding of this zoonosis and to suggest some new approaches to the diagnosis and treatment of the infection.

The clinical course of the acute period of infection is characterised by two phases, an *enteral phase*, in which the parasite alters intestinal function, and a *parenteral phase*, which is associated with an inflammatory and allergic response to muscle invasion by the larval parasites. Gastro-intestinal signs appear first, then fever, myalgia, periorbital oedema, characterise the clinical picture. Death is now rare, owing to improved treatment, but may result from congestive heart failure due to myocarditis, encephalitis, pneumonitis, hypokalaemia, or adrenal gland insufficiency.

A definitive diagnosis may be made when L₁ larvae are found in a muscle biopsy; however anamnestic criteria and laboratory findings such as hypereosinophilia, total IgE, and muscle enzyme level increase may help in diagnosis. The use of newer specific serological tests (enzyme linked immunosorbent assay (ELISA) and immunoblot) can improve diagnosis. Treatment is based

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Abbreviations: ADCC, antibody dependent cellular cytotoxicity; CPK, creatine phosphokinase; ELISA, enzyme linked immunosorbent assay; IL-5, interleukin-5; LDH, lactate dehydrogenase

Table 1 Characteristics of the seven identified *Trichinella* species

<i>Trichinella</i> species*	Muscle capsule	Infectivity for pigs	Freeze resistance	Molecular markers (PCR)	Reported sources	General geographic distribution
<i>T spiralis</i>	+	++++	–	173 bp	Pork; game; horse meat	Cosmopolitan
<i>T britovi</i>	+	+	±	127, 252 bp	Pork; game; horse meat	Temperate Europe/Asia
<i>T pseudospiralis</i>	–	+	–	300, 360 bp	Pork; game	Cosmopolitan
<i>T papuae</i>	–	+	–	240 bp	Pork; game	Papua New Guinea
<i>T nativa</i>	+	–	+++	127 bp	Game	Arctic/subarctic
<i>T nelsoni</i>	+	+	–	155, 404 bp	Game	Africa (south of Sahara)
<i>T murrelli</i>	+	–	–	127, 361 bp	Game; horse meat	North America

*See reference 2 for details. PCR, polymerase chain reaction; bp, base pairs.

have distinct epidemiological and geographical distributions (table 1). Although the species are difficult to differentiate morphologically, they can be typed with molecular and certain biological characters.²

LIFE CYCLE

All stages in the life cycle of trichinella occur in individual mammalian hosts. When skeletal muscle containing the infective larvae is ingested by another mammal, the larvae are released by the action of gastric fluids and pass into the small intestine. There, the parasites invade the small intestine epithelial wall, and moult four times before becoming sexually mature. After copulation, the females begin to expel newborn larvae about six or seven days after infection. This process continues for the life of the female. Although it is generally believed that the adult worms may persist in the intestine for only several weeks, there is evidence that they may survive for much longer periods, especially if the host's immune system is compromised. Most of the newborn larvae penetrate into the submucosa and are carried in the circulatory system to various organs, including the myocardium, brain, lungs, retina, lymph nodes, pancreas, and cerebrospinal fluid. However, only the larvae that invade the skeletal muscle survive. In most species they gradually encyst and develop into the infective stage about 21 to 30 days after infection (fig 1A). However, in two species, *T pseudospiralis* and *T papuae*, the muscle larvae do not induce the formation of a cyst or capsule (fig 1B). Larval infectivity can be retained for many years, depending on the species of host. The larvae appear to be non-pathogenic for the natural hosts (excluding humans) unless very large numbers are involved.

EPIDEMIOLOGY

The most salient feature of this parasite's epidemiology is its obligatory transmission by ingestion of meat. A second cardinal feature is its existence in two normally separate ecological systems, the sylvatic and the domestic.³ In certain circumstances, the two biotopes are linked through man's activities,

resulting in the exposure of humans to *Trichinella* species normally confined to sylvatic animals. The species most frequently associated with human infection is *T spiralis*, the species that is normally found in domestic pigs. The domestic cycle of *T spiralis* involves a complex set of potential routes. Transmission on a farm may result from predation on or scavenging other animals (for example, rodents), hog cannibalism, and the feeding of uncooked meat scraps. Until recently, outbreaks predominantly resulted from consumption of *T spiralis* infected pork in local, single source outbreaks; however, increasingly, the mass marketing of meat can disseminate the parasite throughout a large population. Also of importance is the growing proportion of outbreaks caused by sylvatic *Trichinella* species, either directly through game meat or through spillover to domestic animals. Recent reports also indicate that infected herbivores (horses, sheep, goats, and cattle) have been the source of outbreaks, a new variation on the traditional model of trichinellosis epidemiology. Examples are recent human infections attributed to *T pseudospiralis* in New Zealand in 1994, recently in Thailand where 59 people were infected by pig meat, and in France where an outbreak from wild boar meat occurred in 1999.¹

In countries where meat inspection for trichinella is not mandatory,⁴ other strategies for reducing consumer risk are followed. In the United States, for example, consumers are advised on proper meat handling procedures (for example, cooking, freezing, curing) for killing any trichinella present. Cooking to an internal temperature of 60°C for at least one minute is advised. Consumers are also urged to freeze pork at either –15°C for 20 days, –23°C for 10 days, or –30°C for six days if the meat is less than 15 cm thick. These temperatures may not be adequate, however, for wild game meat infected with species such as *T nativa*, which is freeze resistant. The curing of pork sufficient to kill trichinella is difficult to standardise. Commercial production of ready-to-eat pork products is carried out under scrutiny of regulatory agencies to ensure food safety.

Figure 1 Histological appearance of *Trichinella* species L₁ larvae located in diaphragms of mice experimentally infected. (A) Sample from a mouse infected with *T britovi*. Note around the nurse cell numerous inflammatory cells (trichrome stain; original magnification × 200). (B) Sample from a mouse infected with *T pseudospiralis*. Only few inflammatory cells are present around the L₁ larva (haematoxylin and eosin; original magnification × 200).

PATHOGENESIS

Enteral phase

At intestinal level, the mechanisms regulating the immune response to a primary infection in humans, are not clear. The prolonged diarrhoea observed in outbreaks in the Canadian Arctic^{5,6} suggests adult worms persist in the intestine of people with frequent exposure to infection. This could be due to a possible downregulation of the intestinal immune response or of gut physiology, or to a premunition state.

Experimental studies in rodents infected with *T spiralis* have shown that the early phase of helminthic infection, when the parasite is present in the gastrointestinal tract, induces a type I hypersensitivity reaction, leading to increased levels of mast cells, eosinophils, and parasite specific IgE production. This isotype has a protective role in intestinal immunity in rodents.⁷ Very recently, it was shown that the mucosal mast cell protease-1 plays a crucial part in determining the expulsion of trichinella adult worms, in fact knock-out mice for the corresponding gene significantly delayed expulsion and increased the number of encysted larvae, compared with wild type animals.⁸

In the jejunum of patients infected with *T spiralis* an increased number of mucosal mast cells occurs.⁹

Diarrhoea during infection is a consequence of a physiological process induced by the parasite, resulting in active secretion of ions and water, as occurs with *Vibrio cholerae*.¹⁰

Parenteral phase

This is associated with inflammatory and allergic responses caused by the invasion of the muscles by the migrating larvae. 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.¹¹

The involvement of the central nervous system during infection, the so-called neurotrichinosis, arises mainly from vascular perturbations, for example, vasculitis and granulomatous inflammatory reactions surrounding invading larvae. The newborn larvae tend to wander, causing damage before re-entering the bloodstream, or may remain trapped to be later destroyed by the provoked granulomatous reaction.¹² Neural cells may also be damaged by eosinophil degranulation products such as eosinophil derived neurotoxin and major basic protein.^{13,14}

Myocarditis results initially from muscle cell invasion by the migrating larvae, then from immunopathological processes such as eosinophil infiltration and mast cell degranulation.¹⁵

Immunological aspects

The mechanisms responsible for the pronounced eosinophilia, frequently observed in trichinellosis, are not well understood. Differentiating factors specific for eosinophils such as interleukin-5 (IL-5),¹⁶⁻¹⁸ produced by the Th2 subset of CD4+ T cells, may be involved. Recently, in experimental infections, it has been shown that this cytokine could act by protecting cells from the apoptotic death which normally affects eosinophils.¹⁹ The role of IgE in inducing the eosinophilia is controversial.^{20,21} Eosinophils are cytotoxic for newborn larvae in both animal^{22,23} (fig 2) and human antibody dependent cellular cytotoxicity (ADCC) "in vitro" reactions,^{24,25} by releasing the major basic protein,²⁶ peroxidase,²⁷ or reactive oxygen species.²⁸ However, their actual role "in vivo" is not clear. Suppression of eosinophilia by an IL-5 specific monoclonal antibody "in vivo" does not modify either primary or secondary parasitic infections in mice.²⁹ Knock-out³⁰ and transgenic³¹ mice for IL-5 have the same parasitic burden as controls, however in the former case the cytokine seems to promote expulsion and muscle hypercontractility.

Figure 2 *T spiralis* newborn larva alive within peritoneal cells, from normal mice, adhering to the parasitic cuticle, in the presence of hyperimmune serum, after six hours of incubation (interferential phase contrast microscopy, 1/48 sec; original magnification $\times 1000$; from Bruschi F, *et al*³¹ with permission).

Nevertheless, a very recent study has shown that IL-5 deficient mice show an impaired defence against a secondary *T spiralis* infection, at intestinal level, suggesting a relevant role of this cytokine in challenge infections.³²

The few data on the non-encapsulated species are from experimental infections with *T pseudospiralis*. This species appears to be less virulent and pathogenic than *T spiralis*, generating less inflammation at intestinal and muscle level.³³ This is probably due to the ability of this species to induce elevations in host plasma corticosterone.³⁴

CLINICAL MANIFESTATIONS

The severity of the clinical course depends on the species involved. For example, in the recent outbreak in Thailand caused by *T pseudospiralis*, the clinical course in patients was unusually prolonged.³⁵ Other factors affecting the clinical course are the number of living larvae ingested, and sex, age, and ethnic group of the host.³⁶ Immune status also plays an important part as shown in humans,³⁷ and in experimental infections in which steroids and immunosuppressive treatments prolong the survival of adult intestinal worms.³⁸ Furthermore, the prolonged diarrhoea in the absence of myalgia, reported in elderly Inuit people, may be due to previously acquired immunity against the enteral and parenteral stages of the parasite.^{5,6}

The disease incubation period ranges from seven to 30 days, depending on the severity of infection. When the course of infection is more severe, the incubation period is brief, although death may also occur in association with a longer incubation period.³⁶

The clinical course of the acute period of infection is characterised by two phases, an *enteral phase*, in which the parasite alters intestinal function, and a *parenteral phase*, which is associated with an inflammatory and allergic response to muscle invasion by the larval parasites.³⁹ The first gastrointestinal signs result from mucosal invasion by the L₁ (stage 1) (ingested) larvae. These signs typically last two to seven days, but may persist for weeks. Subsequently, the so called trichinellotic syndrome or general trichinellosis syndrome, begins (see below). However, the acute phase, lasting one to eight weeks, is commonly asymptomatic, especially when the number of larvae ingested is low.

The clinical course of enteral infection may be abortive (symptomatology not complete), mild (complete even if mild), moderate, and severe (frequently associated with

complications).⁴⁰ Malaise, anorexia, nausea, vomiting, abdominal pain, fever, diarrhoea, or constipation may occur. Diarrhoea is more persistent than vomiting, lasting up to three months, and, when excessive, causes dehydration; this, together with enteritis, is an occasional cause of death. Variations in this pattern occur, particularly in relation to a possible premunition state, as already mentioned.^{5 6}

Muscles are mainly affected during the parenteral phase, including the myocardium. The central nervous system, lungs, kidney, and skin may be affected. The trichinellosis syndrome is characterised by facial oedema, muscle pain and swelling, weakness, and frequently fever; anorexia, headache, conjunctivitis, and urticaria occur less frequently.^{36 40} Fever, usually remittent, generally begins at two weeks, and peaks after four weeks, with values up to 40–41°C in severe cases. Despite fever, patients may appear in good condition. Ocular signs (oedema of the eyelids, chemosis, conjunctivitis, conjunctival haemorrhages, disturbed vision, and ocular pain) at this time may help in diagnosis. Periorbital oedema is peculiar to trichinellosis, ranging from 17% to 100% of patients in over 2000 trichinellosis cases reviewed. This oedema is probably the result of an allergic response.⁴¹

The entire face may also be involved, giving patients a characteristic aspect, often rendering them unrecognisable. The frequency of facial oedema during infections caused by *T. murrelli* was lower than that observed in *T. spiralis* human infections that occurred in France in the same year.⁴² At this time the muscles of the rest of the body usually become painful. Extraocular muscles, masseters, tongue and larynx muscles, diaphragm, neck muscles, and intercostal muscles are most frequently infected.

The pain may be so severe as to limit function of the arms and legs, inhibiting walking, speaking, moving the tongue, breathing, and swallowing. Weakness is also a consequence of the muscle involvement. The muscles become stiff, hard, and oedematous; the oedema may be so intense as to simulate hypertrophy.⁴³ Oedema lasts one or two weeks and disappears with increased diuresis. Myalgia and asthenia lasted more than four months in the Thailand outbreak caused by *T. pseudospiralis*.³⁵

Gastrointestinal symptoms such as diarrhoea may also extend into this parenteral phase.³⁶ Dyspnoea (even ventilatory failure),⁴⁴ coughing, and hoarseness may also be present. Dyspnoea is caused primarily by parasite invasion and consequent inflammations of respiratory muscles such as the diaphragm. Bronchopneumonia and infarction may also be involved. In the first days of treatment with albendazole in a *T. pseudospiralis* outbreak difficulty of respiration was observed, probably due to the release of toxic products from damaged parasites.³⁵ The cough begins in correspondence with the passage of the larvae through the capillary bed of the lungs, about one week after infection.⁴⁵

Neurological manifestations, more common in severe infections, occur in 10% to 24% of cases.^{46 47} In 55 patients affected by neurotrichinosis, meningoencephalitic signs were the most frequently observed clinical signs (96%), followed by focal paralysis or paresis (73%), and delirium (71%); psychosis was also reported.⁴⁷

Headache is very common in trichinellosis, and is exacerbated by movements of the head. Mortality due to central nervous system involvement is now less frequent because of the improved treatment.

Myocarditis is the most frequent cardiovascular complication, leading sometimes to heart failure or bronchopneumonia; in some cases death occurs between the fourth and the eighth week of infection, although sudden death may occur even earlier.³⁶ Arrhythmias, secondary to myocarditis, may also occur. In one case it was necessary to use a pacemaker for one year to maintain normal cardiac rhythm.⁴⁴ Electrocardiographic alterations may be present from the second week and may persist up to the third or fourth week. The principal

alterations are premature contractions, prolongation of the P-R interval, small QRS complexes with intraventricular block, and flattening or inversion of the T waves, especially lead II and precordial leads.

Blood pressure may be low during the early phase of infection and may also remain low during convalescence. Oedema due to heart failure has been observed, generally later when oedema due to myositis has almost disappeared. Less frequent vascular signs are epistaxis, haemoptysis, haemorrhages from the bowel, thrombosis of the femoral or pulmonary artery, and embolism. In one fatal case, the arterioles of different organs were affected by disseminated intravascular coagulation with platelet fibrin thrombi.⁴⁸ Less frequent are petechial haemorrhages, mainly subungual, and roseola and maculopapular exanthems, resembling measles.⁴⁵

After the acute period, convalescence follows (lasting from months to years), usually with a complete recovery. Over the ensuing years, muscle larvae are slowly destroyed, followed by calcification.⁴⁹ This may occur earlier in infections with sylvatic species.⁵⁰

The existence of chronic trichinellosis⁵¹ or as some investigators prefer, “persisting sequelae”⁵² (the persistence of myalgia, early fatigability, ocular signs, and headache for decades), is somewhat controversial and requires investigations. Some recent studies have confirmed the occurrence of these sequelae for periods up to 10 years after clinical recovery.^{52–54}

Although death is now rare in trichinellosis, owing to improved treatment, it may result from congestive heart failure due to myocarditis, encephalitis, pneumonitis, hypokalaemia, or adrenal gland insufficiency.^{36 45} In the United States, during the period 1991–96, in 230 cases reported to the Centers for Disease Control in Atlanta, only three deaths occurred.⁵⁵ During the outbreak caused by *T. pseudospiralis* in Thailand there was one fatality in 59 patients, due probably to the very large amount of parasite-infected meat ingested.³⁵ During a horsemeat outbreak in France, caused by the newly described *T. murrelli*, a 0.46% mortality rate was observed.⁴² No deaths were reported in outbreaks caused by *T. britovi*.

DIAGNOSIS

Is trichinellosis a low prevalence disease or is it frequently misdiagnosed? The answer is not obvious.

When the infection occurs in epizootic or outbreak form its diagnosis is easier. It is difficult in low level or sporadic infections, because the clinical picture is often common to many other diseases, infectious or not, such as typhoid fever, influenza, chronic fatigue syndrome, myositis during HIV infection, polyarteritis nodosa, and eosinophilic leukaemia. This makes it necessary to carry out a differential diagnosis.

Special care must be taken when developing clinical histories; particular attention should be paid to eating habits during the weeks before the onset of symptoms. Exposure to infected meat (raw or incompletely cooked), the presence of gastroenteritis, myalgia, facial oedema, subungual or conjunctival haemorrhages, and an increase in eosinophil levels should suggest trichinellosis.³⁶ Electromyography may help in the diagnosis of moderate and severe infections during the acute period, even if the muscle changes are not pathognomonic. With clinical improvement, electromyography changes generally disappear within two to three months,³⁶ although these alterations may persist for one to eight years.⁵⁷

Muscle biopsy

A definitive diagnosis may be made when L₁ larvae are found in a muscle biopsy, generally performed in the deltoid muscle; although in humans other muscles are more infected, the deltoid is preferred because it is more accessible.⁵⁸ Muscle biopsy is recommended only in rare and difficult cases, particularly when serology is not clear. A negative result, however, does not

Table 2 Laboratory findings in human trichinellosis

Constant	Exceptions	Frequent	When	Rare	When
Hypereosinophilia* (up to 19 000/μl)	Very severe infections; coinfections with bacteria	Leucocytosis, up to 24 000/μl CPK (up to 17 000 units/l), LDH , aldolase level increase Total IgE level increase	Early in severe infections Parenteral phase with muscle damage Parenteral phase mainly	Eosinopenia Hypoalbuminaemia (down to 25 g/l)	After steroid therapy Severe infections or infections caused by <i>T pseudospiralis</i>

Parameters useful in diagnosis when modified are shown in bold.

*Based on the absolute number rather than the percentage.

exclude the presence of a low level infection.⁵⁹ Artificial digestion (1% pepsin-hydrochloric acid) of a muscle sample is more sensitive than direct microscopic observation of the tissue specimen. Importantly, the isolation from muscle cannot be carried out before 17 to 21 days of infection because larvae are not yet resistant to digestion.⁶⁰ When *T pseudospiralis* or *T papuae* (non-encapsulating species) are suspected as aetiological agents, digestion methods must be performed with care.⁶¹ A muscle biopsy is useful, however, not only for making a diagnosis but also to collect important information on the level of infection, the pathological changes in the muscle tissue, the infection time, and for genetic typing (by random amplified polymorphic DNA analysis of the parasite).⁶² This is important when the source of infection is unknown or no longer available. Molecular techniques allowed for the first time the identification of *T pseudospiralis* in a human trichinellosis case in Tasmania.⁶³ All such information is useful for the choice of future therapeutic strategies.³⁶

Histological examinations may reveal modifications of skeletal muscles, including basophilic degeneration of the fibres, fatty metamorphosis, hyaline or hydropic degeneration, or both, and interstitial inflammation; sometimes it is possible to observe dead non-encapsulated parasites.³⁸ Increased vascularity, small haemorrhages, accumulation of inflammatory cells, mainly eosinophils, among the muscle cells (myositis) are also visible.^{64 65}

Encapsulation of the parasite, with the exception of *T pseudospiralis* and *T papuae*, begins at about two weeks and is usually completed at five weeks of infection,³⁸ depending on the *Trichinella* species involved.³⁰ In humans, calcification begins about five months after infection and is usually completed after 18 months.³⁸

As already mentioned, the diagnosis of trichinellosis is difficult in sporadic cases, but is even more difficult when central nervous system involvement is present. Neurotrichinosis is sometimes accompanied by multifocal central nervous system lesions, nodular or ring-like, and showing frequently contrast enhancement.^{14 66} However, computed tomography images of the brain have been normal also in the presence of neurological manifestations.^{66 67}

LABORATORY FINDINGS

Non-specific findings

The main laboratory findings useful for diagnosis are shown in the table 2.

Muscle enzymes such as creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) may remain raised for more than four months, as occurred in >90% of patients affected by *T pseudospiralis* in Thailand.³⁵

CPK isoenzyme profiles are not very helpful. An increased CPK isoenzyme-MB level, generally ascribed to myocardial damage, has been observed in 35% of trichinellosis patients examined, with no cardiological symptoms, suggesting a release of this isoenzyme from other damaged striated muscle

cells.⁶⁸ LDH should be evaluated together with CPK, even if the former is less specific. When high levels of CPK and LDH are present, a differential diagnosis with myopathies is necessary. Before antibody levels increase, the level of total serum LDH and the isoenzymatic forms LD₄ and LD₅ may increase in about 50% of patients.⁶⁹

Immunoglobulin level changes may also occur, the most characteristic being an increase in total IgE. However, this increase is not a consistent phenomenon and it is better to not exclude trichinellosis by its absence.⁵⁹ A poor correlation with specific IgE has been observed in *T spiralis*⁷⁰ and *T britovi*⁷¹ infections.

Specific findings (immunodiagnosis)

Many serological tests are available for diagnosis.^{59 60} According to Ljungström there are three objectives in immunodiagnosis: (1) recognising the acute infection to allow early anthelmintic treatment, (2) making a retrospective diagnosis, and (3) adding information to the epidemiology of the infection.⁷² Seroconversion usually occurs between the third and fifth week of infection and serum may remain positive up to one year or more after cessation of clinical symptoms. Antibodies have been detected, however, up to 19 years after the end of the acute phase of infection.⁷³ Antibody levels do not correlate with the severity of the clinical course⁶⁹ nor with a particular clinical course.⁷⁴

Indirect haemagglutination, bentonite flocculation, indirect immunofluorescence, latex agglutination, and enzyme linked immunosorbent assay (ELISA) are the more commonly used tests, the last being the most sensitive.⁵⁹ Factors such as sensitivity, specificity, convenience, simplicity, cost, and commercial availability must be considered when choosing a test. However, a diagnostic laboratory should have at least two or more tests available to ensure a correct diagnosis: one to detect the response against a soluble antigen and another for antibodies that react with parasite surface antigens.⁷² For the latter, the indirect immunofluorescence test is performed with whole L₁ larvae killed with formalin,⁷⁵ or with unfixed frozen sections of infected muscles⁷⁶; the latter is more sensitive. With this test all specific immunoglobulins can be evaluated. In the ELISA method,⁷⁷ excretory-secretory (E/S) antigens are preferable to crude extracts of *T spiralis* muscle larvae, since they give a higher specificity. This is particularly important in tropical regions where cross reactions with other helminth parasites could give false positive results.^{78 79} Cross reactions with trichinella antigens were observed in patients with autoimmune diseases.⁸⁰ It is necessary to standardise as much as possible the antigens used for diagnostic purposes.^{81 82} Recombinant⁸³ or synthetic⁸⁴ antigens have been developed. The ELISA can also be used for the evaluation of the different immunoglobulin classes⁸⁵⁻⁸⁷ or IgG subclasses⁸⁸ of antibodies, but with a lower sensitivity compared with ELISA IgG. Specific IgM has been detected after 11 years of infection.⁸⁷ The data on specific IgE are contradictory.^{78 85 86} Circulating antigens are also not completely reliable.⁸⁹ They were found in 47% of

Table 3 Treatment for intestinal and muscle stages of trichinellosis

Symptomatic treatment	Specific treatment
Analgesic drugs	Mebendazole 200–400 mg three times/day, followed by 400 to 500 mg three times a day for 10 days
Antipiretic drugs	Albendazole 400 mg/day for three days, followed by 800 mg/day for 15 days (is particularly efficient in <i>T pseudospiralis</i> infections)
Bed rest Corticosteroids (prednisolone at 50 mg/day)	Thiabendazole 50 mg/kg for five days

From references 98–100.

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patients with clinical trichinellosis and in 13% of patients suspected of infection; healthy subjects with no history of trichinellosis were negative. In comparison, the indirect immunofluorescence test and a competitive inhibition assay were more sensitive (100% positivity for the sera of the above cited patients).⁸⁹ However, the presence of circulating antigens indicates the actual presence of the parasite, eliminating the need for muscle biopsy. Immunoblotting^{90–91} can be considered a confirmation test and when E/S antigens are used it is quite specific and useful for follow up studies⁹²; however it cannot determine the species of trichinella responsible for infection.⁹²

The analysis of the cellular immune response in humans is of little value at present for diagnosis.^{87–93}

TREATMENT

It is difficult to differentiate the efficacy of drug treatment from natural recovery of infection in mild to moderate cases. Factors such as the *Trichinella* species involved, intensity and length of infection, and host response can aid in deciding on the treatment course.^{36–94}

Light infections do not require treatment. The treatment goal for the very early infection phase is to limit muscle invasion by larvae; when this has already occurred the goal is to reduce muscle damage, which is responsible for the major clinical manifestations. Therapeutic plasma levels of the drug should be maintained for an extended period, rather than high levels for short periods.⁹⁵ The success of treatment is evident from clinical improvement of the patient's symptomatology. In a blinded, placebo controlled trial of antiparasitic drugs for the treatment of myositis during a trichinellosis outbreak (Thailand), mebendazole and thiabendazole were more efficient than placebo or fluconazole; however 30% of volunteers did not tolerate the side effects of thiabendazole.

Questions (answers on p 22)

1. Is trichinellosis always derived from the ingestion of undercooked pork containing *Trichinella spiralis*?
2. Will freezing meat (for example –15°C for 20 days) kill any muscle larvae present?
3. What is neurotrichinosis?
4. What is the cause of myocarditis during trichinellosis?
5. Can the presence of high levels of total IgE help in the diagnosis of trichinellosis?
6. Are eosinophils responsible for the protective response against trichinella?
7. Which factors can modify the clinical course of trichinellosis?
8. Can trichinellosis be lethal?
9. Can a negative muscle biopsy exclude the diagnosis of trichinellosis?
10. Which serological test can be used to confirm the diagnosis of trichinellosis?

The authors did not mention the *Trichinella* species responsible for infection.⁹⁶ When muscle larvae are already encapsulated drugs such as mebendazole are not able to control infections very well.⁹⁷

In infections caused by *T pseudospiralis* albendazole (800 mg/day in four doses) is particularly efficient, without apparent side effects (see table 3).³⁵

PROGNOSIS

As already mentioned, the prognosis is usually good with the exceptions of the rare, heavily infected cases. The seriousness of the infection depends on the number of ingested larvae and on the elapsed time before the diagnosis has been made and treatment begins.

CONCLUSIONS

The recent occurrence of new *Trichinella* species, such as *T murrelli* and *T pseudospiralis*, in outbreaks in humans, could render the clinical picture of trichinellosis more complicated than when all infections were believed to be caused by *T spiralis*. Clinicians and infectious disease specialists should consider this when making diagnosis, since the clinical signs and symptoms may differ, and the therapeutic choices be less clear.

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Answers

1. No, human infections have resulted from ingestion of many kinds of meat in addition to pork. In Europe, for example, over the past 20 years, thousands of cases have resulted from improperly cooked horse meat, wild boars, and even dog meat. All seven species of trichinella have been involved in outbreaks, although most pork derived cases involve *T spiralis*.
2. Generally, such freezing is effective. However, wild game meat from the arctic and subarctic regions may contain *T nativa*, which is highly resistant to freezing. In these regions, such meat should be cooked well.
3. This term is used to indicate the involvement, possibly with clinical manifestations, of the central nervous system during infection caused by the parasitic nematode of trichinella genus.
4. We have to distinguish the early phase of infection when migrating larvae may play a relevant part by attempts to invade myocardial muscle and the late phase when immunopathological processes cause a myocardium damage.
5. As in other helminthic infections, total IgE levels may be increased. However, trichinellosis cannot be excluded even when IgE is at normal levels. Furthermore, anamnestic, clinical, and serological data are necessary to make diagnosis of infection.
6. Despite the great amount of research using “in vitro” experiments, which showed the ability of these cells to kill parasites in ADCC systems, experiments using both transgenic and knock-out mice for IL-5 have clearly shown that eosinophils play little, if any, part in the immune defence against a primary infection with this parasite.
7. As observed in *T britovi* and *T pseudospiralis* outbreaks, the species of trichinella involved, as well as the number of parasites ingested, are quite important factors. However, host characteristics, such as sex, age, and immune status may also be important determinants of clinical outcome.
8. Death due to trichinellosis is rare, thanks to improving of diagnostic aids and the availability of proper treatments, however when a large number of parasites are ingested or the diagnosis is not made quickly, fatal cases can still occur.
9. Muscle biopsy is at present the best way to make a diagnosis when parasites are present, however in cases of very low infections it is possible that parasites are absent in the tissue fragment obtained. In this case a specific and sensitive serological test is valuable in the diagnosis.
10. After an initial serological diagnosis, usually by an ELISA or an immunofluorescence assay, the use of a test such as immunoblot can be useful to confirm the diagnosis.