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Diagnostic algorithm in human trichinellosis - premise of avoiding complications and chronicity of the disease

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Abstract. *Aim of the study: a systematic review of the scientific literature that contains theoretical information about the infection with Trichinella species in humans. The research questions were formulated, the criteria for inclusion and exclusion of the revised studies and the search strategy were established, the studies were selected, the data were extracted and finally the analysis and interpretation of the results was performed, all with the aim to establish a diagnostic algorithm for patients with the suspected trichinellosis. From 312 existing studies, 300 that did not meet the inclusion criteria were excluded. The theoretical aspects studied refer to the clinical and laboratory criteria that validate the diagnosis of trichinellosis in humans and focus less on the elements of differential diagnosis, which would facilitate early diagnosis and allow the establishment of specific antiparasitic treatment removing the spectrum of complications or progression to chronicity of the disease.*

Keywords: systematic review, trichinellosis, scientific literature.

Introduction

Trichinellosis is a zoonosis that is frequently found in the sylvatic, peridomestic and domestic environment, in animals such as bears, wild boars, foxes, field rats and pigs from households or from small animal farms. The disease is transmitted to humans by eating pork or game meat infected with the Trichinella spiralis parasite, which is incompletely or incorrectly heat-treated (Gottstein et al. 2009). In humans, the disease has a tropism for striated muscles, where the parasite, after a long process of evolution, can survive up to 40 years (Fröscher et al. 1988). Undiagnosed trichinellosis and therefore untreated in a timely manner can progress chronically, socially and professionally incapacitating the patient. Hence the importance of an early diagnosis of human trichinellosis, which will mean the inactivation of the parasite in the circulatory spread phase of the diseases or in the beginning of its encystment (Dupouy-Camet et al. 2007, Gottstein et al. 2009).

In humans, the Trichinella spiralis parasite goes through 3 stages from infection to encapsulation. The first enteral phase begins with the ingestion of infected meat. In the stomach of the new host the larvae become free and pass very quickly into the small intestine, where it finds both food and oxygen necessary for their growth and development. The larvae deposited by the females of the parasite spread through the circulatory system, throughout the body, in their migration to the striated muscle. The

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second phase, of circulatory dissemination, allows the larvae of Trichinella spiralis the possibility to reach the striated muscles, the most irrigated, where it finds conditions for development and encapsulation. The third phase of the disease usually corresponds to the third week of evolution, when the parasite is encysted in the striated muscles (Kociecka 2000, Pozio et al. 2003, Gottstein et al. 2009).

Methodology

In the present study, a systematic review of the scientific literature regarding human trichinellosis was performed, which followed the plan described below:
Formulation of the research questions or hypothesis:
What signs and symptoms,
What laboratory tests,
What elements of differential diagnosis,
What complications,
What evolution of the disease,
What elements of chronic trichinellosis appear mentioned in the literature on human trichinellosis?
Criteria for including the revised studies:
- To refer exclusively to human trichinellosis,
- Theoretical general reports, guides or reviews,
- To describe the subjective and objective clinical symptoms in humans,
- To propose a laboratory diagnostic algorithm in human trichinellosis,
- To be written in Romanian, English and French,
- To be studies in extenso,
- 1996-2019 was the period for which the documentation was made.

Criteria for exclusion of studies:
- To refer to the animal trichinellosis.
- Presentations, posters at unpublished scientific events.
- Case presentations or outbreaks in humans.
- The abstract of the research, in case the full text was not available.
- Duplicate studies.

Search strategy: systematic searches, over several years, in the literature databases: Proquest Academic, Science direct, Springerling, Web of science, Medline / Pubmed. The keywords for the search of articles were: trichinellosis and human, Trichinella spiralis and human, clinical trichinellosis, chronic trichinellosis, human trichinellosis and chronic trichinellosis, outbreaks of trichinellosis, outbreaks of trichinellosis and trichinellosis.
Selection of studies: duplicate studies were eliminated and studies meeting the inclusion and exclusion criteria were selected. The final selection of studies was made on the basis of the full text. Studies of interest have been translated from English and French.
Data extraction was performed by dividing the studies into categories: epidemiology of trichinellosis, clinical disease, differential diagnosis, complications, outbreaks, and chronic trichinellosis.
The analysis and interpretation of the results was performed by creating tables in Microsoft Excel that included: signs and symptoms of the disease, laboratory tests, elements of differential diagnosis, complications, evolution, signs of chronic trichinellosis.

Results and discussions

By systematically reviewing the literature, out of 312 studies, we excluded 300 that did not meet the pre-established inclusion conditions. Finally, a number of 12 studies were identified, which refer strictly to the theoretical notions of Trichinella infection in humans and in which we found answers to the research questions (table no. 1).

Table no 1. The articles selected by a systematically review the literature

No.	Name of articles, authors and year of publication
1	Clinical aspects of infection with Trichinella spp V. Capó, D.D. Despommier, 1996
2	Clinical aspects, diagnosis and treatment of trichinellosis E. Pozio, M.A. Gomez Morales, J. Dupouy-Camet, 2003
3	Epidemiology, Diagnosis, Treatment, and Control of Trichinellosis B. Gottstein, E. Pozio, K. Nöckler, 2009
4	Nonbacterial Myositis N.F. Crum-Cianflone, 2010
5	Parasitic infections and myositis. S.N. El-Beshbishi, N.N. Ahmed, S. H. Mostafa, G. A. El-Ganainy, 2012
6	Uncertainties in diagnosis, treatment and prevention of trichinellosis. Z.Shimoni, P. Froom, 2015
7	FAO/WHO/OIE Guidelines for the surveillance, management, prevention and control of trichinellosis J. Dupouy-Camet, K.D. Murrell, 2007
8	Opinion on the diagnosis and treatment of human trichinellosis. J. Dupouy-Camet, W. Kociecka, F. Bruschi, F. Bolas-Fernandez, E.Pozio, 2002
9	Trichinellosis: human disease, diagnosis and treatment W. Kociecka, 2000
10	Management and diagnosis of human trichinellosis, J. Dupouy-Camet, F. Bruschi, 2007
11	New aspects of human trichinellosis: the impact of new Trichinella species. F. Bruschi, K.D.Murrell, 2002
12	Areas of uncertainty in the management of human trichinellosis: a clinical perspective G. Wattand Udomsak Silachamroon, 2004

Source: Authors' own research.

In the attention of the teams that performed the studies, in the foreground are the clinical aspects of the disease, then the data provided by laboratory tests and their complications. The differential diagnosis, although an important aspect for the early establishment of antiparasitic treatment, is not a chapter of interest like the evolution of the disease itself, including the transition to the chronic stage of the disease.

In the 12 studies related to trichinellosis, 9 symptoms are described in the enteral phase of the disease, 30 symptoms and 14 signs in the migration phase. The most common symptoms are: periorbital and/ or facial edema, high fever, myalgia, followed by diarrhea and subconjunctival, subungual, and retinal hemorrhages.

No study has been concerned with correlation of the symptoms described by the patient with the evolutionary stage of the Trichinella spiralis parasite in the body. It would have been important because, from our practical experience, it has been shown that the patient with trichinellosis goes to the doctor most frequently during the circulatory dissemination of larvae, when he recognizes in recent history a number of moderate digestive or respiratory symptoms, but this does not determine him to go to a general practitioner or to a specialist physician (Nemet et al. 2013, Dobrescu et al. 2014).

Theoretically, if we extract from the symptoms described by the patient those of the onset for which he did not see a doctor, the following symptoms remain relevant: chills, high fever, asthenia, excessive sweating, general weakness, malaise and low fever, insomnia. We point out that, in the specialized literature, the association of malaise with low fever is found at the beginning of the disease, even in the enteral phase (Kociecka, 2000, Dupouy-Camet et al. 2002). High fever, chills, apathy, asthenia are symptoms that accompany the patient in the evolution of the disease from the period of circulatory dissemination to the phase of encapsulation in the striated muscles.
In the case of the digestive tract, dysphagia is relevant for the presence of the parasite in the striated muscles of the pharynx, denoting the circulatory dissemination phase (Kociecka, 2000, Gottstein et al. 2009).
The respiratory system recognizes dry cough, coryza, hoarseness, as well as symptoms of systemic spread of Trichinella larvae (Dupouy-Camet et al. 2007, Gottstein et al. 2009).
The cardiovascular system registers rhythm disorders, given that the parasite at the end of the enteral phase and the beginning of the circulatory dissemination has a mandatory cycle through the atrium, thus affecting the cardiac-type striated muscles of the myocardium (Dupouy-Camet et al. 2002, Dupouy-Camet et al. 2007, Gottstein et al. 2009).
The nervous system notices headaches, various sensory disorders, apathy, aphasia, dizziness, irritability, symptoms that may occur due to the nature of systemic trichinellosis in the period of circulatory dissemination phase and may prolong in convalescence and for long periods of time.
The sense organs are highlighted by periorbital and/ or facial edema, visual and auditory disorders, retinal hemorrhage, photophobia, symptoms that are significant in the circulatory dissemination phase of the parasite.
Skin manifestations such as various rashes, rash, petechiae, edema of the limbs, subungual hemorrhages are characteristics during the course of the disease (Kociecka, 2000, Dupouy-Camet et al. 2007, Gottstein et al. 2009).
In the muscular and skeletal system, the symptoms are expressed by localized or generalized myalgias, pain in the movement of the eyeballs, difficulties in opening the mouth, which explains the fact that the larvae have reached the striated muscles where they find their encapsulation locus. This ends their phase of circulatory migration and causes malfunctions trough location. Myalgias may persist in varying degrees of intensity even during convalescence or for indefinite periods of time suggesting a possible course to the chronic stage of trichinellosis (Kociecka, 2000, Dupouy-Camet et al. 2007, Gottstein et al. 2009, Shimoni et al. 2015).
From the analysis of the signs of the disease that the doctor detect during the objective examination, in the researched studies, our hypothesis is confirmed that usually trichinosis is detected in the systemic dissemination phase of the parasitic infection. The patient, through the exposed symptoms, only described it as a history and offered the doctor the possibility to develop from the first consultation a suspicion of trichinellosis if he combines the symptoms with clinical signs and completes them with the epidemiological link: consumption of infected pork.
The authors do not describe any objective signs belonging to the digestive tract, which means that the patient presentation at the medical consultation is not made in the enteral stage of the disease, which is the first stage of the parasite in its evolutionary cycle in humans.
Eosinophilia is a typical response to nematode infections coming from laboratory tests and this is also valid in trichinellosis. Eosinophilia is the earliest and most characteristic

laboratory finding of trichinellosis and has been observed in nearly all cases, with the exception of people with very mild trichinellosis and people with trichinellosis complicated by a secondary bacterial infection (Pozio et al. 2003). Eosinophilia appears early prior the development of clinical signs and symptoms, between the second and the fifth week of infection in practically every case of trichinellosis, with only few exceptions recording the maximum values in the third week of the disease (Gottstein et al. 2009). Various degrees of eosinophilia have been observed: low (<1000 μl), moderate (1000–3000 μl) and high (>3000 μl) and up to 19,000 cells per microliter have been reported (Pozio et al. 2003). Even among asymptomatic cases eosinophilia reaches modest levels (5 to 15% of leukocytes) *(*Capo et al. 1996). During the acute stage of infection, a massive decrease in eosinophil levels in persons with severe trichinellosis can be considered to be a predictor for a severe outcome. Several studies have shown that eosinophilia seems to be correlated with the intensity of myalgia and the number of newborn larvae and is significantly greater in people with neurological complications (Capo et al. 1996, Gottstein et al. 2009). For these reasons, it is a valuable diagnostic criterion.

Eosinophilia regresses slowly and can remain at low levels for a period of several weeks to 3 months. During the acute stage of the disease a sudden reduction in the level of circulating eosinophils in persons with severe trichinellosis predicts a grave course of the disease (Capo et al. 1996, Kociecka 2000, Pozio et al. 2003). A sudden reduction in the level of circulating eosinophils to 1% or none is an indication of severe infection and may even signal the onset of death of the patient (Capo et al. 1996, Pozio et al. 2003). Eosinophilia is mentioned in all the theoretical articles that have been studied.

Leukocytosis is characteristic of the acute stage of trichinellosis and indicates the presence of inflammation. It is not as frequent as eosinophilia, yet it is present in a large number of people, especially those with severe infection (Pozio et al. 2003). The high leukocytosis appears early and rapidly increases between the second and fifth week of the disease and may reach 15,000–50,000 per mm^3 (Kociecka 2000, Pozio et al. 2003).

Leukocytosis appears early and increases simultaneously with eosinophilia; however, whereas eosinophilia may remain high for 6–8 weeks, leukocytosis regresses more rapidly, with the acute signs disappearing. Recurrences of leukocytosis have been observed and are associated with complications, such as thrombophlebitis and pneumonia, which are typical of severe trichinellosis. Nonetheless, at times, people with severe trichinellosis can develop lymphopenia (Pozio et al. 2003, Gottstein et al. 2009).

As a result of the damage to muscle tissue by the migration of newborn larvae, the muscles release *enzymes* into the circulation, increasing the serum levels of these enzymes. These enzymatic disturbances mainly involve creatinophosphokinase (CPK) and lactate dehydrogenase (LDH). Increased CPK activity has been observed in 75–90% of infected people and most frequently occurs between 2 and 5 weeks after infection. LDH activity has been reported to increase between the first and sixth week of muscle invasion and peaks earlier with respect to antiTrichinella antibodies (Kociecka 2000, Pozio et al. 2003). No relationship has been observed between severity of the clinical course and the augmented activity of LDH (Kociecka 2000). There is no relationship between enzymatic disturbances and the severity of the clinical course of the disease (Pozio et al. 2003, Gottstein et al. 2009).

The principal electrolyte disturbance is hypokaliaemia, which results in reduced muscle strength and cardiac disturbances, as revealed by ECG. Decreased levels of proteins

and albumin, which are usually detected at the late stage of severe infection, result in a hydrostatic edema. These disturbances should be treated by counterbalancing the water, electrolyte and protein deficits (Kociecka 2000, Pozio et al. 2003).
Although the presence of larvae in muscles almost always produces bioelectric disturbances, as revealed by electromyography, these disturbances are not pathognomonic for trichinellosis. The disturbances reveal muscle lesions and are characterized by a decreased amplitude of muscle contraction and incomplete interference. The disturbances regress simultaneously with clinical improvement and with the subsiding of histological lesions in muscle tissue. In most people, bioelectric disturbances occur at the acute stage and correspond to the severity of the clinical course and to the intensity of the disease. However, disturbances have also been observed several years after the acute stage in people with chronic trichinellosis, who, as mentioned, are those who had not been treated in a timely manner. Bioelectric disturbances in a single individual are characterized by a combination of electrical alterations, including disturbed motor-neurone function and impulse transmission at the neuromuscular junction (Kociecka 2000, Pozio et al. 2003).
Augmented activity of aspartate aminotransferase is not seen in every case of trichinellosis, but may supplement the clinical evaluation of trichinellosis patients (Kociecka 2000).
Trichinellosis, like other helminth infections, is characterized by increased levels of serum immunoglobulins, hypergammaglobulinemia, mainly immunoglobulin E and immunoglobulin G (Kociecka 2000, Pozio et al. 2003). The scientific literature points out that the detection of specific anti-Trichinella antibodies in blood serum has a special diagnostic value, in total contradiction with our opinions. Current practice has shown us that the serological diagnosis is relevant at 2-3 weeks of illness, which can late confirm our clinical suspicion of trichinellosis, and thus its importance in the early diagnosis of the disease on which depends the establishment of specific antiparasitic treatment is illusory (Nemet et al. 2008, Balescu et al. 2013).

Conclusion

In most cases trichinellosis is detected in the systemic phase of parasitic infection. The doctor can develop the suspicion of trichinellosis from the first consultation if he combines the symptoms with the clinical signs and completes them with the epidemiological link: consumption of infected pork.
Among the laboratory tests, eosinophilia is characteristic of trichinellosis, which is observed in all cases.

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