Central Nervous System in Trichinellosis

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Trichinellosis is a parasitic disease caused by the consumption of raw meat infected with larvae of nematode in the genus Trichinella.

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1. Overview

We reviewed the evidence on features of central nervous system (CNS) involvement in trichinellosis, systematically searching five databases (to January 2021). We categorized clinical features based on their diagnostic value as warning signs for severe CNS infection (with outcome death) or non-specific signs (outcome improvement). They were suggestive of severe infection if they substantially raised death probability. The review included 87 papers published from 1906 through 2019, with data on 168 patients. Mydriasis, paraparesis, dysphagia, psychomotor seizures, or delirium present a 30–45% increased death likelihood. The best poor prognosis predictor is mydriasis (positive likelihood ratio 9.08). Slow/absent light reflex, diminished/absent knee reflexes, globally decreased tendon reflexes present a moderate increase (20–25%) of death risk. Anisocoria, acalculia, or seizures could also indicate an increased death risk. We provided a detailed presentation of clinical and paraclinical signs that alert physicians of a possible neurotrichinellosis, emphasizing signs that might indicate a poor prognosis.

2. Trichinellosis

Trichinellosis is a parasitic disease caused by the consumption of raw meat infected with larvae of nematode in the genus *Trichinella*. The first report about the new findings of *Trichinella* was presented to the zoological society in London in 1835, when Sir Richard Owen, and his student, Sir James Paget, discovered the parasite during an autopsy [1]. Friedrich von Zenker reported the first acute case of human trichinellosis in 1860 [2]. He presented the dissemination mode of the parasites in the host by implicating the consumption of raw, infected pork as the vehicle of transmission. In 1906, Frothingham reported evidence of the central nervous system (CNS) involvement [3]. Later observations revealed the presence of *Trichinella* in the cerebrospinal fluid (CSF).

Human trichinellosis was reported in 55 (27.8%) countries around the world. *Trichinella* infection was documented in domestic animals, mainly in pigs, in 43 countries, and the wildlife of 66 countries [4]. A systematic review, including data between 1986 and 2009, reported an estimated global incidence rate of 469.2 to 985.3 cases per billion persons per year. The global mortality rate was 0.300–0.828 per billion persons per year [5].

The global distribution of *Trichinella* infection mirrors the geographical distribution of parasites in domestic animals (i.e., pig, horse, dog) and wild animals (i.e., boars, bear, badger, cougar, jackal, walrus, lizard and turtle), the dietary habits (i.e., eating raw meat), and the social and economic development of the countries [6][7]. After 1990, the socioeconomic changes in some Eastern European countries and Argentina, determined the reemergence of *Trichinella* infections in these areas. Nonetheless, in the last years, there was a significant decrease of the number of cases reported in the European Union countries, the United States, Canada and China [8]. Despite a general reduction of the number of cases with *Trichinella* infection, which is mainly due to the development of systematic regulations regarding the domestic animals (pigs), there has been an increase of the number of Trichinellosis cases due to the consumption of wild animals [7]. In the last decades, important *Trichinella* outbreaks were reported in South East Asia countries (e.g., Cambodia, Thailand, Vietnam) and South America (e.g., Argentina) [6]. In Africa, there is a low prevalence of human *Trichinellosis*, possibly due to the dietary and religious habits [4]. However, despite the religious laws forbidding the consumption of pork, *Trichinellosis* was also documented in Muslim countries such as Turkey [4].

After ingestion, under the influence of gastric secretions, the *Trichinella* larvae are released in the stomach and develop in the adult stage inside the enterocytes of small intestine. The newborn larvae are released into circulation, spreading

through the tissues and organs. *Trichinella* spp. has an intracellular localization only in two different tissues, specifically, in enterocytes and skeletal muscle cells. It has a unique ability to transform the infected muscle cell and create a new type of cell in the host body, the so-called nurse cell [9]. From this place, the parasite induces the formation of muscle larvae excretory-secretory products (ES L1). The invasion of the host generates a complex immune response, which is better characterized by humoral rather than cellular responses (hence the importance of humoral response for diagnostic purposes) [10]. During the intestinal phase, the immune response includes both Th1 and Th2 responses. Initially, it induces a Th1 responses, followed by a dominant Th2 type of response. This later type of immune response is characterized by the production of high levels of cytokines IL-4, IL-5, IL-9, IL-10, IL-13, immunoglobulin E (IgE), and the mobilization of eosinophils, basophils, and mast cells [11]. The existence of Treg cells further characterizes the muscle phase. The chronic stimulation through ES L1 released during the muscle phase of *Trichinella* infection activates regulatory network elements. Immune events induced by Th2 and Treg cell types modulate the immune response of the host [11].

The *Trichinella* infection is characterized by peripheral blood and tissue eosinophilia and an increased total IgE levels, both being a consequence of Th2 activation. Eosinophilopoiesis begins in the bone marrow, followed by the migration of eosinophils through the circulatory system, infiltration of tissues with eosinophils at the inflammatory foci and, finally, degranulation, and cell death [12]. However, the protective role of eosinophiles against *Trichinella* remains under debate. Furthermore, when the number of eosinophils is increased, they can be toxic to host tissues.

The *Trichinella* antigens stimulate dendritic cells and macrophages to interact with T cells. Activated T cells produce cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3 and IL-5. They will determine the proliferation and differentiation of precursors into eosinophils. The migration of the eosinophils from the bone marrow to the vessels is controlled mainly by IL-5. The *Trichinella* antigens might attract and affect eosinophils directly to interact with T cells. In addition, the alternatively activated macrophages (AAMs) also attract eosinophils through chitinase-like molecule (Ym1) and arginase 1 (Arg1). In addition, eosinophils are attracted by Galectin 9 (Gal-9), eotaxin-1, and eotaxin-2. The eosinophils around *Trichinella* in the tissues produce cytokines, cytotoxic secretory products, growth factors, lipid mediators, and neuro-mediators. These molecules were reported to play a role in larval killing, tissue injury, or tissue repair, together with various cells. The involvement of eosinophils in worm expulsion from the gut is still uncertain. Nonetheless, the increase of activated eosinophils is responsible for damage to the vascular walls probably because of the release of the major basic protein, which is elevated in patients with eosinophilia. Additionally, it explains tissue damage in the CNS and other tissues [12].

The clinical picture of *Trichinella* infection is heterogeneous, varying from asymptomatic to fatal, depending on the number and sites of larvae. The symptoms parallel the parasite cycle and the responses of the host. The first infection stage consists of non-specific gastroenteritis, occurring two to seven days after ingestion of infected food. The larva migration and invasion determine the characteristic clinical signs and symptoms of *Trichinella* infection. Larvae and their products cause a diffuse inflammatory reaction, with fever, headache, rash, focal edema, local inflammation, leukocytosis, and eosinophilia. The most affected muscles are the extraocular muscles, masseters, diaphragm, intercostals, deltoids, tongue, larynx, and neck muscles. In severe cases, diffuse and severe muscle involvement manifests with myalgia, especially of the diaphragm, calves, and forearms. Additionally, a characteristic finding is increased muscle consistency, with weakness [1].

The most severe complications are related to the CNS, heart, and lungs [13]. The CNS involvement was reported in 10–20% of patients and is usually associated with severe *Trichinella* infection. The reports on mortality vary between 8% [14] to 46% [15]. However, with the treatment with corticosteroids and benzimidazoles (e.g., mebendazole and albendazole), the number of fatal outcomes has decreased.

The clinical manifestations of CNS trichinellosis comprise diffuse encephalopathy and focal neurologic deficits. Cerebral invasion occurs during the second week, the larval migratory stage. The patients present with varying degrees of meningoencephalitis manifested by non-focal clinical signs. Focal CNS lesions occur during the third week, the encystment stage. The clinical signs often overlap with previous meningo-encephalitic symptoms. Only rarely are they the sole manifestation and include motor deficits (e.g., hemiparesis), cranial nerve deficits, cerebellar signs, aphasia, and seizures [13]. Additionally, patients may present occlusion of cerebral venous sinus, causing venous infarction or intracerebral hemorrhage [16]. Patients with focal brain damage may present significant diagnostic challenges, mainly if they are first seen with a focal cerebral picture.

The meningeal form frequently causes minimal mental and focal signs, while in the parenchymal form, patients present marked mental and focal signs with minimal meningeal involvement [13].

The Centers for Disease Control (CDC) case definition for trichinellosis comprises: (1) *Trichinella*-positive muscle biopsy or positive serologic test for trichinellosis in a patient with a clinical syndrome compatible with trichinellosis (including eosinophilia, fever, myalgia, and periorbital edema) or (2) in an outbreak, at least one person must meet criteria 1, with associated cases defined by a positive serologic test for trichinellosis or clinical symptoms compatible with trichinellosis (including eosinophilia, fever, myalgia, and periorbital edema) in individuals who shared the epidemiologically implicated meal or have consumed the implicated meat product [17].

The case definition for trichinellosis at the European Center for Disease Control states, “at least three of the following six: fever, muscle soreness and pain, gastrointestinal symptoms, facial edema, eosinophilia, and subconjunctival, subungual, and retinal hemorrhages” [10][17].

The differential diagnostic difficulties rarely arise in cases of “typical” acute trichinellosis. However, the cases with CNS involvement may represent a diagnostic challenge, especially in the lack of eosinophilia. In addition, the presentations of CNS infection are myriad, and the diagnosis can be elusive [18].

The drugs of choice in *Trichinellosis* are anthelmintics (albendazole or mebendazole). They should be given before the initiation of corticosteroids to prevent the effect of delayed expulsion of adult worms from the intestine. Their efficacity depends on the time delay between infection and the beginning of treatment, and it is likely dose-dependent [19]. Although no valid controlled studies have been performed, corticosteroids are frequently used to treat allergic manifestations, which occur at the beginning of the parenteral phase [10]. The corticotherapy is strongly recommended to suppress the vascular and muscle damage induced by eosinophil degranulation products [20]. In severe cases, corticosteroids were reported to reduce the course of the illness [21]; after their implementation, the number of fatal cases with neurological involvement has decreased significantly [19]. In addition, the neurological complications occurring in the early period of the illness were reported to be successfully treated with corticosteroids. Still, when these complications appear after one month, they can cause permanent sequelae [19].

In addition, practical recommendations have been published for severe and moderately severe diseases [10].

In the latest years, experts have developed risk-based approaches to control the presence of parasites in meat, requiring the re-evaluation of traditional practices and the assessment of regulatory and industry resources. In 2020, the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) published a report that provides spreadsheet models to get quantitative information needed by public health officials when evaluating different post-mortem hygiene programs for *Trichinella* spp. in meat [22]. These models enable the development of risk scenarios to assess the effect of changes to digestion testing and meat inspection on the risk of human Trichinellosis [22]. Applying the latest risk-based approach recommendations requires a re-evaluation of traditional practices and assessing regulatory and industry resources proportionate to risks. In addition, the link between control measures pre-and post-harvest along the food chain and public health outcomes will help risk managers locate the source of the infection at the farm, abattoir, processor, and consumer level for food safety interventions, according to the publication [22]. In addition, there are international recommendations for quality assurance in digestion testing programs for *Trichinella* [23]. Additionally, many countries have specific regulations for the inspection and control of the parasite, and there are different treatment methods to inactivate *Trichinella* larvae in meat, including cooking, irradiation, and freezing for some genotypes.

The present research aimed to systematically review and summarize the existing evidence on the CNS complications of *Trichinellosis* infection, described in case reports and case series. Although a case report provides only a descriptive result, systematic reviews of multiple cases allow narrative or quantitative synthesis, pattern recognition, and identification of unrecognized or rare associations. Furthermore, it can generate hypotheses for subsequent studies and advance medical knowledge.

3. Discussion

The present systematic review enabled us to make several key observations.

The most frequent clinical features of the CNS involvement in *Trichinella* infection consist of some non-specific meningo-encephalitic findings, such as headaches, confusion, spatial and temporal disorientation, and meningeal signs, including neck stiffness and Kerning signs. Additionally, patients may present focal brain damage, indicated mainly by motor deficits, most frequently hemiparesis. Tendon reflexes might be brisk or diminished, and the Babinski sign is also present in almost one-quarter of the patients. Cerebellar and cranial nerve involvement is relatively rare, and so are seizures.

Psychiatric and behavioral disturbances are not very frequent. Cognitive impairments consist mainly of deficits in recent memory [20][24][25][26][27][28][29], resembling Korsakoff syndrome and aphasia [20][30][31][32][27][33][34][35][36].

Interestingly, in patients who died, the headache, neck stiffness, and positive Kerning sign rates were quite similar to those with a favorable outcome. However, delirium was present in almost half of the deceased cases (41.17%), compared to 9.87% in the group of all patients. Additionally, the tendon reflexes were diminished in almost half of the patients with unfavorable outcome. Among 24 patients with decreased knee tendon reflexes, 11 died. Mydriasis and absent or slow light reflex were reported in a higher percentage of patients who died than patients with improvement. (17.65% mydriasis and 17.5% slow light reflex vs. 3.09%, respectively 4.94%). Among 13 patients with mydriasis or impaired light reflex, six of them died.

The clinical signs with an LR+ between 5 and 10, indicating an increased chance of death with 30–45%, included mydriasis, paraparesis, dysphagia, psychomotor seizures, and delirium. The best predictor of a poor prognosis was mydriasis (LR+ of 9.08). Although some clinical signs such as diminished knee reflexes [13][37] and absent or slow light reflex [37] were earlier postulated to indicate a poor prognosis, we found them to present a moderate increase in death risk of 20–25%: diminished or absent knee reflex (3.02), globally decreased tendon reflexes (3.46), slow or absent light reflex (4.03). Additionally, we found that anisocoria, acalculia, or seizures could also indicate an increased risk of death.

Interestingly, clinical findings that usually for a neurologist are red flags, such as bilateral Babinski sign, lethargy, stupor, or positive Kerning sign, present a low LR+.

The CSF findings were normal in 44 (41.12%) patients. The rest of the samples presented mainly increased pressure (10.28%) and increased proteins (14.95%). In most cases that presented cells in the CSF, they were leucocytes (14.95%). Glucose levels were abnormal in 5.6% of cases. *Trichinella* larvae were found in less than one-quarter of the patients (18.69%). In patients who died, CSF was normal in 40%, the pressure and glucose levels were normal in 80%, cells were in a normal range in 60%, and proteins were found normal in 70% of cases. Therefore, the absence of pathological findings in CSF does not exclude a poor prognosis.

Blood eosinophilia was present in 89.58% of all cases. Nonetheless, approximately half of the patients who died (45.45%) did not present an increase in eosinophils count. Therefore, it may be postulated that a lack of eosinophilia indicates a poor outcome in patients with a severe symptomatology [38], but further investigation of this paraclinical parameter is necessary.

The CT findings in neurotrichinellosis are non-specific, with multiple hypodensities in the white matter. Nonetheless, a normal CT scan does not exclude CNS involvement. The imaging method of choice should be MRI, which is more sensitive in assessing the extent of brain damage. Border-zone brain lesions may be indicative of neurotrichinellosis. In particular, a patient with eosinophilia and border-zone ischemic lesions should be investigated for idiopathic hypereosinophilic syndrome or brain infection (trichinellosis, filariasis, or schistosomiasis) [39][36][40]. As indicated by autopsy reports, the majority of lesions are situated in the white matter. Notably, lesions of the thalamus, cerebellum, and brain stem were less frequent. In addition, rim or nodular enhancement suggests a possible neurotrichinellosis.

Our systematic review included a comprehensive literature search, including articles published in the last 115 years. Nevertheless, our findings are limited by the quality and breadth of the data in the case reports, which was not uniform or consistent in all papers. In addition, after 1969, the antihelmintic treatment introduction could have hypothetically modified the clinical picture of cerebral trichinellosis. Nonetheless, the clinical signs reported in neurotrichinellosis after this date were relatively similar to previous cases. Although the number of deaths decreased, it is noteworthy that the clinical signs that we found as indicating a poor prognosis were reported more rarely.

Most importantly, the analysis of case series and reports can suggest hypotheses. Therefore, clinicians should be aware of the large number of cases reported in the literature and the multitude of CNS manifestations. The evidence provided should alert physicians of the possible CNS involvement in trichinellosis infection and some clinical signs that might indicate a poor prognosis. However, further studies are necessary for the diagnostic value of clinical and paraclinical features of neurotrichinellosis to identify severe CNS infection.

Despite the limitations mentioned above, our study represents the first systematic review of the literature published in this field and outlines an accurate state of knowledge of cerebral and meningeal implications in acute *Trichinellosis*.

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