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Review article

Toxocarasis and the Epilepsy as Clinical Process in Childhood

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Abstract

The Helminths are still a highly prevalent cause of disease in the world, especially toxocariasis, which results from the infection of Toxocara canis and Toxocara cati. The infection by these parasites occurs accidentally, leading the human being into becoming intermediate hosts of the life cycle. Toxocariasis can present itself in different ways, according to the place where the larva is lodged. This review evaluated epilepsy as an outcome of toxocariasis in pediatric patients. The bibliographic review of the scientific literature was carried out in the library of the Centro Universitário do Planalto Central Professor Apparecido dos Santos (UNICEPLAC), as well as in the PUBMED, MEDLINE, LILACS and COCHRANE databases. Articles in English, Portuguese and Spanish were considered, without date restriction. The course of neurological symptoms results from post-treatment complications, due to the direct presence of the larva in the Central Nervous System (CNS) and/or tissue inflammation, with the outcome of focal (related to granulomas) or generalized (associated with immunological reaction) seizures. Other common manifestations are sleep and behavioral disorders or meningoencephalitis with different prognosis. Laboratory and imaging tests, such as computed tomography and nuclear magnetic resonance, stands out for the diagnostic method. Therefore, the use of antiparasitic drugs, as well as parasitic control in dogs and cats, are an important form of treatment. Neurotoxocariasis is not yet fully elucidated as a complication of toxocara infection, especially when it is associated with epilepsy. Thus, it is necessary that further studies are carried out in order to understand the effects of this parasitosis in patients of preschool and school age.

Keywords: Epilepsy. Toxocariasis. Childhood.

Introduction

The development of the state of the art in health has provided over the years the control of several diseases around the world. However, several others, despite a vast therapeutic arsenal, continue with a high prevalence, as it is the case of helminthiasis (FINSTERER, 2007).

A helminth disease of great relevance to health due to its high frequency is the infection by Toxocara canis and Toxocara cati (KAYES, 1997; KWUNG FAN, 2015). The genus Toxocara belongs to the phylum Nemathelminths, class nematoda, order ascaroidea, superfamily Ascaridae (KWUNG FAN, 2015).

The development of these roundworms has the following stages: anembryonic eggs, embryonated eggs, larvae in three stages (L1, L2 and L3) and the adult worm (HALLACK and CUNHA, 2005). These parasites can complete their cycle only in dogs and cats (definitive hosts - adult worm in the intestine. However, they can infect humans as an intermediate host (BEAVER, 1962).

Morphologically, adult worms have a cylindrical, elongated and thin body, sexual dimorphism, - (the mouth is at the anterior end and the cloaca at the distal end, and a complete digestive system (REY, 1991).

Infection in humans occurs by ingestion of embryonated eggs with larvae in the L3 stage, which travel to the small intestine where they hatch and penetrate the intestinal wall, proceeding to the lungs via the portal circulation. However, if the larvae are larger in diameter than the vessels, they perforate the wall of these and can migrate to different tissues such as the brain (GLICKMAN and SCHANTZ, 1981).

Toxocara canis larvae periodically change their cuticles, which are formed by proteins. These cuticles are released into the circulation and can hinder the action of the host antibodies (KAYES, 1997).

The first description of this helminthiasis occurred in the early 1950s, but its occurrence remained underestimated for many years (MAGNAVAL et al., 2001). Currently it is known that it reaches expressive levels throughout the terrestrial globe. Population growth represents a risk factor for Toxocara infection by increasing contact between humans and definitive hosts, but its frequency is even more significant in rural areas (MAGNAVAL et al., 2001).

Another relevant variable in the epidemiology of this disease is socioeconomic, and the less favored classes have a higher prevalence (ANARUMA FILHO et al., 2002).

In human toxocariasis, T. canis is more important as an etiological agent (TONELLI et al., 2005) presenting in several clinical forms, and can be classified according to Pawlowski (2001) as systemic (classical or incomplete), compartmental and hidden.

The systemic form or Visceral Larva Migrans Syndrome (VLMS) may present with pulmonary symptoms, hepatosplenomegaly, fever, eosinophilia, hypergammaglobulinemia, and it usually occurs in the incomplete

form with only some of these symptoms. The most common compartmental forms are ocular toxocariasis (OLMS – Ocular Larva Migrans Syndrome) and neurological toxocariasis (NLM – Neurological Larva Migrans). The occult is poorly diagnosed and may present only nonspecific symptoms such as abdominal pain, pain in the lower limbs and hepatomegaly (TONELLI et al., 2005).

Although neurological toxocariasis is not the most common form of presentation of this helminthiasis, it is extremely relevant due to the severity of the symptoms it can cause and the fact that their reversibility or not is essentially determined by early diagnosis and treatment. Manifestations can involve both the central (CNS) and peripheral (PNS) nervous systems, including: epilepsy, dementia, myelitis, meningoencephalitis, cerebral vasculitis, radiculitis, musculoskeletal involvement and cranial nerve aggression (FINSTERER et al., 2007).

LMN is also an important differential diagnosis of several neurological disorders, and should always be considered in investigations to mitigate the chances of underdiagnosis (FINSTERER et al., 2007).

Diagnosis is based on clinical manifestations and laboratory data obtained through blood count (eosinophils > 2,000/mm^3) and ELISA (Enzyme-Linked Immunosorbent Assay) test, which is based on antigen-antibody reactions, with positive serology being the most important marker of human infection by Toxocara, as it is present in all types of patients, whether they are asymptomatic or carriers of more severe forms (TONELLI et al., 2005).

The treatment of toxocariasis is performed with anthelmintics such as thiabendazole (50mg/kg for ten days) and albendazole (15mg/kg for five days). Antihistamines, bronchodilators and corticosteroids can be used in the acute phase to relieve symptoms (TONELLI et al., 2005).

For Pawlowski (2001), the specific treatment of toxocariasis in VLMS and LMO seeks to reduce the number of larvae migration to the brain and eyes during the course of the infection.

The current scientific literature has few studies that address the issues of the neurological consequences of toxocariasis, especially with epilepsy as an outcome. Therefore, this review seeks to compile existing information on the subject to assess the impact of neurological outcomes of toxocariasis in childhood, trying to consolidate the knowledge that already exists about epilepsy caused by this helminthiasis, which has a high seroprevalence, but is still neglected in the world, and its manifestations in pediatric patients.

Development

This is a narrative literature review that analyzes epilepsy resulting from toxocariasis and its neurological impacts in pediatric patients. In its production, active searches were carried out in the theoretical collection from the library of the Centro Universitário do Planalto Central Professor Apparecido dos Santos (UNICEPLAC); in addition to searches in the PUBMED, MEDLINE, LILACS and COCHRANE databases. The descriptors children were used; nervous system; Toxocara canis; toxocariasis; epilepsy. Only articles in English, Portuguese and Spanish, without date restrictions, due to the limited amount of published material on the topic, were selected. The literature review was carried out in the 2nd semester of 2020, until the month of November.

The ingested larvae are released into the intestine in the second stage of Toxocara (L2), when they are able to cross the intestinal mucosa and use the lymphatic system to reach the portal circulation and the liver, then through the blood circulation they reach the lungs from where they will reach the entirety of the organism via the hematogenous route. However, during this migration, the larvae grow and, as they become larger than the capillaries, cross their walls and migrate through the tissues, during which time they are metabolically active and releasing secretion-excretion antigens (TES). Therefore, at the beginning of the infection, there is an acute inflammatory reactionwhere granulomas may form (REY,1991). However, despite the intense inflammation and immune response, Toxocara larvae can survive for long periods and can be reactivated and remigrate (KAYES, 1997).

The pathogenesis of human toxocariasis is complex and can be influenced by several factors such as: the host's immunological condition and its sensitization to products secreted by the larvae, the amount and frequency of ingestion of eggs/larvae and the presence of larvae in the tissues, triggering inflammation. Thus, the main manifestations are the result of direct tissue damage caused by migration and inflammation (CARVALHO, ROCHA, 2011).

Serological studies in population groups show a predominance of seropositivity for toxocariasis in children, due to the greater practice of geophagy in this age group. Considering the pediatric group, studies established a higher prevalence of infection in males (ANARUMA FILHO et al., 2002).

According to Z. Pawlowsky (2001), the clinical manifestations appear in a wide spectrum, which can be: asymptomatic, Visceral Larva Migrans Syndrome – VLMS (classic systemic), occult and compartmentalized (ocular and neurological).

Most clinical presentations are asymptomatic. In situations that present as Visceral Larva Migrans Syndrome (VLMS), it is common to find general symptoms, ranging from mood deterioration to fever. In addition to the liver, the main site of installation, where larvae tend to die after a period, other organs can be affected, such as the lungs, as well as cardiac and skeletal muscles (KAZEK et al., 2006).

The atypical presentation of toxocariasis in which neurological impairment occurs, despite not being the most common outcome, is important due to severe clinical manifestations and the possibility of permanent damage if not identified early, which leads to great social losses, especially when we talk about pediatric patients who may have compromised normal development (FINSTERER et al., 2007).

The seroprevalence of Toxocara canis in children is around 60% in developing countries according to some studies (KAZEK et al., 2006), but it is known that a relevant number of children are not diagnosed and treated, and it is in this context that cases with neuropsychological damage occur more frequently (MARMOR et al., 1987).

An epileptic seizure is a transient occurrence of signs and/or symptoms that occur as a result of synchronous or excessive neuronal activity in the brain, which may be sudden and transient abnormal phenomena - changes in consciousness, or motor, sensory, autonomic or psychic events. involuntary movements that are perceived by the patient or an observer (THURMAN et al., 2011). Epilepsy is a brain disorder in which there is a persistent predisposition to generate epileptic seizures/attacks (KAZEK et al., 2006).

Epilepsy can be classified as idiopathic (undetermined cause) or secondary (causes can be congenital, trauma, infections, among others).

The development of neurological symptoms in toxocariasis can occur due to post-treatment complications, the direct presence of larva in the Central Nervous System (CNS) and/or tissue inflammation, which can lead to focal (granuloma-related) or generalized, which is associated with immunological reaction (AKYOL et al., 2007). Sleep and behavioral disorders or myelitis, meningoencephalitis may also occur, and these have a more reserved prognosis (KAZEK et al., 2006; LUNA et al., 2018).

Radiculitis, although rarer, is another outcome that can occur in neurotoxocariasis, usually manifesting in association with meningitis, and its diagnosis is made through clinical findings (muscle weakness, reduction of tendon reflexes), changes in cerebrospinal fluid (CSF) - antibodies against T. canis, eosinophilia, and abnormal nerve conduction (FINSTERER et al., 2007).

KAZEK et al. (2006) report that Toxocara canis is the known infectious agent that most causes epilepsy, reaching a ratio of six to

one when compared to the causative agent of cysticercosis. Most of the infected have clinical symptoms related to the immune reaction due to the inability to contain the infection.

Toxocariasis can lead to the development of immune vasculitis and this, when severe, can cause irreversible neurological deficits, even if the course of the underlying disease is benign. In general, vasculitis in cerebral toxocariasis is more intense in the white matter of the brain and cerebellum, the same distribution also occurs in the case of granulomas (KAZEK et al., 2006).

According to the study by MARMOR et al. (1987), children infected with toxocara presented worse performance in different tests than uninfected ones, and parents of children with helminthosis reported hyperactivity in children, which did not occur in the disease-free group (control). But, despite the study sample being small, and the study not determining the temporal sequence between infection and neurological damage, it serves to alert to the need for more prospective studies on the topic. Likewise, KAZEK et al. (2006) reinforce the importance of education and awareness of parents of young children and dog owners, since the former represents part of the risk group and the latter a "source of contagion" when parents allow their animals to remain infected.

The relationship between toxocariasis and epilepsy is difficult to demonstrate significantly with seropositivity for T. canis alone, but they seem to be generally associated, which leads to think of the parasite as a cofactor in the development of epilepsy in children with some predisposition (ARPINO et al., 1990).

Even today, the diagnosis of this helminthiasis is complex, although serological tests are more available, as the infection can present with typical, atypical or asymptomatic symptoms (LUNA et al., 2018).

In cases of Visceral Larva Migrans Syndrome (VLMS), the diagnosis involves laboratory, clinical, ultrasound and immunodiagnostic factors. It is common to find persistent eosinophilia, enlargement of abdominal parenchymal organs, abdominal lymph node enlargement, recurrent bronchitis, dry cough and granuloma. In cases of Ocular Larva Migrans Syndrome (OLMS), blindness (usually unilateral) can be found, most commonly coursing with vitreous inflammation, traction of vitreoretinal filaments towards the optic nerve, cystoid macular edema and/or a granuloma (CARVALHO, ROCHA, 2011).

In cases of neurotoxocariasis, it is possible to find increased brain levels of IgG (ARPINO et al., 1990), as well as, to the analysis of the cerebrospinal fluid, high level of proteins (KAZEK et al., 2006).

In imaging studies of patients with focal epileptic symptoms, areas of low density can be found on computed tomography and T2-weighted images by magnetic resonance (KAZEK et al., 2006).

Laboratory Enzyme-Linked Immunosorbent Assays for anti-T. canis proves to be decisive in the diagnosis of toxocariasis (KAZEK et al., 2006). Positive serological results are the most significant predictors that corroborate human infection with toxocara, whether in asymptomatic, symptomatic or severe patients (TONELLI et al., 2005).

Treatment is indicated in all cases of toxocariasis, which is justified by the clinical characteristics of the patient and/or in a preventive manner (CARVALHO, ROCHA, 2011).

According to PAWLOWSKI (2001), the most used treatment in toxocariasis is albendazole (three times a day). This drug has greater penetration into the CSF, reaches higher serum concentrations and is less toxic, but it is known that other benzimidazole components oxibendazole, flubendazole or thiabendazole) can also be used (FINSTERER et al., 2007). The use of ivermectin is not recommended in the treatment of this helminthiasis (MAGNAVAL et al., 2001).

Neurotoxocariasis can also be treated as monotherapy with thiabendazole or combined with a corticosteroid. Optic neuropathy caused by T. canis is highly sensitive to treatment with corticosteroids; However, the possibility of increasing the number of parasites in the Central Nervous System should be noted. Furthermore, in cases of endophthalmitis, cyclosporine A may be effective (FINSTERER et al., 2007).

Pharmacological treatment is effective, but not sufficient for the complete prevention of this helminthiasis. In this context, one cannot forget the need to prevent recontamination (through the deworming of pets - dogs and cats) and the implementation of health education for the population (MAGNAVAL et al., 2001).

The prognosis of this infection in most patients is benign, despite the larvae living in the host for many years. On the other hand, Visceral Larva Migrans Syndrome (VLMS) compromises many clinical factors and systems, which can mimic a number of other diseases. However, in the absence of diagnosis, in delayed diagnoses or in the absence of specific treatment, the evolution of this helminthosis can cause hepatic, pulmonary and nervous impairment, which can lead to the patient's death (CARVALHO, ROCHA, 2011).

Conclusions

The development of protocols to combat helminthiasis across the planet is still lacking, especially in relation to the consolidation of health measures in underdeveloped and developing countries. These actions include the control and treatment of host animals and the establishment of effective basic sanitation programs for vulnerable populations. Thus, it is observed that the prevalence of seropositivity of these diseases in humans remains high and the occurrence of complications is a public health problem to the present day.

Clear criteria and epidemiological aspects are defined for the diagnosis and screening of patients with toxocariasis, especially in the most prevalent groups, that is, those in the pediatric group, because in these patients the clinical repercussions are diverse, some potentially irreversible and of different prognoses.

Through the literary analysis carried out, it is concluded that it is necessary to carry out more studies aimed at the neuropsychiatric impacts of toxocariasis in children, focusing on the impacts on psychosocial development and on the possible complications caused by epilepsy in these patients, seeking more results related to the neurotoxocariasis.

Our opinion is supported by what was said by ARPINO et al. (1990), that one cannot fail to consider and exclude the diagnosis of toxocariasis in preschool-age children with occasional epileptic seizures or epilepsy before classifying them as of idiopathic nature.

List of abbreviations

ELISA: Enzyme Linked Immunosorbent Assay
L1: First stage larvae of Toxocara
L2: Larva in the second stage of Toxocara L3 - Larva in the third stage of Toxocara CSF - Cerebrospinal fluid
NLM: Neurological Larva Migrans
OLM: Ocular Larva Migrans
VLMS: Visceral Larva Migrans Syndrome OLMS - Ocular Larva Migrans Syndrome CNS - Central Nervous System
PNS: Peripheral Nervous System
T. Kennels: Toxocara kennels
TES: Secretion-Excretion Antigens

Conflicts of Interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

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