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Toxocariasis: a review

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Abstract
Human toxocariasis is a parasitic infection caused by the ingestion of larvae of dog nematode Toxocara canis and less frequently of cat nematode T.cati. In this review, current information about human toxocariasis which is a rare but an important problem suspected to cause rheumatologic, dermatologic and respiratory system diseases, is presented.

Keywords: Toksokariazis, toxocara canis, toxocara cati

Introduction

Toxocara type parasites can cause an infection recognized as ***Toxocariasis*** where helminths of the *Ascarioidea* family that are included in the Nematodea branch, Secernentea class, Ascarioidea set are the main cause. Human toxocariasis may develop due to two main *Toxocara* species. Toxocariasis is an illness of humans caused by larvae (immature worms) of either the dog roundworm (*Toxocara canis*) or the cat roundworm (*Toxocara cati*). Recent studies report that the most frequent factor in human cases is *T. canis* while *T. cati* can be rarely seen [1]. Additionally, a few more Toxocara species are described lately in domestic pets such as cats and other members of the *Felidae familia.* Among these, *T. malayasiensis* can affect domestic cats while *T.lyncus* can affect wildcats. Nevertheless, we still do not exactly know if these species cause a disease in humans [1,2].

Toxocara canis was first described by Werner at 1782 and was named as *Lumbricus canis* [3]. In 1947 Perlingiero and Gyorgy presented the disease as a brand new syndrome in children that developed with manifestations such as fever, hepatomegaly, hepatic granulomatosis lesions, chronic hypereosinophilia, hyperglobulinemia and pulmonary alterations [4]. In 1952, Beaver reported three children with hypereosinophilia and similar long term multiple system involvement and described many clinical symptoms of VLM in such patients; and named the etiological agent determined in histopathological cross-sections obtained by biopsy *Toxocara* [5]. As stated above, Toxocariasis usually affects children under age 10. Especially at risk are those who like to put things in their mouths, or kids whose families have pet dogs or cats.

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Morphology of The Parasite

Egg

Oval structured eggs, are almost the same size of the eggs of *Ascaris* species (74-80 µm) and are colored dark Brown [6,7].

Larva

The larva that hatch from eggs with an embryo is approximately 290-350 µm in length and has a diameter approximately 14-20 µm. *A.lumbricoides* larvae is longer (550-650 µm) and wider (24-26 µm).

Mature

The length of a mature *T.canis* male can vary between 4-10 cm. There are no any ala and a gubernaculum at the tail. A mature *T.canis* female is about 6-18 cm in length. There parasites have both two sex organs. A number of one and a hundred of mature *T.canis* parasites can be found in the intestines of an infected dog and daily thousands of eggs are excreted in feces [6,7].

Life Cycle

Life cycle in cats and dogs

Infection process begins by ingesting infective *Toxocara* eggs when held at appropriate terms and conditions in an external environment and ingested by dogs and cats

through the gastrointestinal route. The larva in the egg with an embryo hatches out in the small intestines of a cat and dog and penetrates itself to the intestinal mucosa. After then it firstly migrates to the liver, then the heart, lungs and another organ by the circulatory system. During the tracheal migration larva can pass into the trachea from the lungs by the means of the bronchus and reach the pharynx where it is ingested the second time, and finally can reach the intestinal cavity. After a three week period, the larva may complete it's development in the small intestines of dogs and cats and become a mature parasite. Male and female mature parasites in the small intestines can mate and eggs without an embryo can generate. A mature female can lay approximately 200.000 eggs/daily without an embryo. It was reported that 10.000-15.000 eggs can exist in one gram of feces of an infected dog [1,6,7].

Mature parasites are reported to live approximately four months on host animals and then usually excreted from the host before six months [3,7]. The eggs are considered not infective when excreted in dog and cat feces. Embryo development shall occur in soil in the presence of appropriate temperature (15-35 °C), moist (%85) and oxygen. Eggs can remain alive under soil for months if they are protected from sunray. Furthermore, it is also reported that eggs can be transported to different areas via rain water [1,7,8].

Life cycle in human beings and other living creatures

The disease shall begin to emerge in human beings or other living creatures after infective (embryo developed) *Toxocara* eggs are digested by the oral route. Eggs with an embryo shall open up to the small intestines of these living creatures and after then free larva's shall penetrate themselves into the intestinal mucosa. Later on they shall pass to the portal circular system from the mucosa and then reach the liver, and after then to other tissues and organs by the means of vascular structures. However, these larvae cannot turn back to the intestines to mature, as it happens in cats and dogs. Larvae shall survive only in the tissue they have located themselves and remain unchanged. When this life cycle of the parasite cannot be completed in such hosts as explained above, then the host is called a "*paratenic host*". Based on the point of view of *Toxocariasis*, paratenic hosts can be human beings and animals such as a mouse, earthworms, ticks, chicken, sheep's, pigs and birds. The life cycle of the parasite is completed when digested by paratenic hosts, dogs or cats [1,6,7,9].

Clinical Symptoms

Despite that very different symptoms and findings can be observed in patients diagnosed with *Toxocariasis*, surprisingly the majority of patients can be asymptomatic. The degree of harm caused by the parasite to the host, combined with clinical symptoms and findings, may vary due to the organs affected by the parasite, the intensity of the infection and it's duration. Factors related to the host such as age and immunity status and the number of larvae immigrated into tissues can have a great impact on the clinical course of the disease [1,6,10].

The clinical outlook of *Toxocariasis* is classified in accordance with the affected organ. These are recognized as visceral larva migrans (VLM) which includes organ diseases and ocular larva migrans (OLM) which displays limited symptoms and findings related to ophthalmological involvement [1,11]. The latter can be seen mostly in children and is considered as a latent toxocariasis.

Visceral Larva Migrans (VLM)

VLM is syndrome that may develop mostly in children due to definite non-human host larvae together with non-systemic and non-specific multiple various clinical symptoms , accompanied with findings such as fever, weight loss, delay in growth, asthma, and gastrointestinal symptoms, and clinical tables related with epilepsy, various non-systemic and non-specific clinical symptoms, findings and laboratory data [12]. Eosinophilia, hypergammaglobulinemia of immunoglobulin M (Ig M), Ig G and Ig E may usually be observed.

Ocular Larva Migrans (OLM)

Granulomas can develop when *Toxocara* larvae reach and locates themselves in the eye. Consequently, intraocular pressure may increase and visual disorders, pain and photophobia may occur. Localized or peripheral granulomas can cause deformity by dragging the retina and lead to heteropia and separation in the macula. *Toxocara endophthalmitis* can easily occur even after a single larva reaches the eye by vascular access. Additionally, certain disorders such as uveitis, papillitis, keratitis, optic neuritis and a vitreous abscess may develop [1, 13].

Latent Toxocariasis

Latent toxocariasis, is a toxocariasis syndrome which emerge as an absolute, complicated ve non-specific clinical symptoms and findings which do not fit in any of VLM and OLM categories, but somehow looks like the both of them, and is observed mostly in children. Non-specific symptoms and findings can include fever, headache, abdominal pain, muscle and joint pain, anorexia, nausea, vomiting, lethargy, sleeping and behavioral disorders, pharyngitis, shortness of breath, coughing, pneumonia, lymphadenopathy, hepatomegaly, fatigue, allergic dermal rashes and chronic itching [14].

Epidemiology

Toxocariasis is a frequently seen infection is an illness of humans caused by larvae (immature worms) of either the dog roundworm (*Toxocara canis*) or the cat roundworm (*Toxocara cati*). Transmission of *Toxocara* to humans is usually through ingestion of infective embryonated eggs of T.cati and canis. This infection is usually seen in places with a mild temperature and hot climate and where bad hygienic conditions are present, and cats and dogs

wandering aimlessly around and appropriate temperature, moist and soil conditions are present for the development of eggs with an embryo [6].

In the USA, a ratio of 13.9% seropositivity was found in a study carried out on a number of 20.395 patients where children were over six years of age [15]. In a study carried out by Rubinsky-Elefant et al., in 2008 at Brazil, Amazon Forest, *T.canis* IgG seroprevalance was reported as 26.8% [16]. In another study carried out by Fan et al., at 2004 in Taiwan, seropositivity was reported 76.6% among 329 children whom were 7-12 years old [17]. Muradian et al., at 2005 in Brazil found a seropositivity of 26.9% in a study carried out in 338 children whom were 1-15 years old [18]. *Toxocara* seroprevalance was reported as 2.4% in 3247 healthy individuals in a study carried out by Stensvold et al., [19] at 2009 in Denmark; while Nicoletti et al., [20] reported seroprevalance at a ratio of 6.6% among 201 healthy individuals in Italy at 2008; and Park et al., [21] reported a ratio of 5.1% among 314 healthy individuals in Italy at 2002; and finally Genchi et al., [22] reported a ratio of 3.98% among 2112 healthy individuals in Italy at 1990.

Transmission route to human beings

Transmission of *Toxocara* to humans is usually through contact with soil contaminated with infective *Toxocara* eggs, infected domestic cats and dogs, or consuming and digesting contaminated food and beverage. It is also reported that transmission of the disease can be by ingestion of larvae as a result of eating raw or less done meat of paratenic hosts. Contact with contaminated soil, has a higher risk regarding contamination when compared with direct contact with infected cats and dogs. The reason here is that first of all, *Toxocara* eggs must spend a certain time at appropriate temperature and moist soil until an embryo is generated [1,4].

Pathogenesis And Immunity

The pathology behind VL is related with the larvae-induced mechanical damage in the host and consequently the immunopathological reactions that may occur. Death of the larvae in tissues can trigger the initiation of hypersensitivity reactions. Inflammation shall display itself by eosinophilic granulomas in the host. Dominant cell type is macrophages when they were neutrophils and eosinophil at further periods. Multiple eosinophilic abscesses and allergic-type eosinophilic granulomas may occur in affected tissues. If the number of parasites is low, then the reason of this could be related with stimulated immunity and thereby the low ratio of antibody formation and the larvae can now freely migrate. As the heavy Toxocariasis infection stimulates a strong immune response, the larva restrict in the liver, lungs or other organs.

Toxocara larvae can stimulate both humoral and cellular immunity systems in the body. During the disease, previously IgM levels may increase, but after then IgG levels may escalate at the next term. However, as observed in entire parasitary diseases, total IgE antibody and peripheral eosinophil levels may increase [1,23].

Diagnosis

Recurrent hypereosinophilia, leukocytosis, hypergamaglobulemia, increased total IgE level, increased isohemagglutinin titer, increased erythrocyte sedimentation rate (ESR) , elevated liver enzyme levels and infiltration in lung graph are non-specific lab findings that can be observed in this disease [1,8,12,24].

An absolute diagnosis of a *Toxocara* infection can be made by biopsy, but on the other hand, biopsy may be assumed as an impractical method due to the presence of *Toxocara* larvae in the histological assessment of infected tissues and the difficulty experienced during diagnosis (Figure 1). *Toxocara* larvae cannot reach a mature form in human beings and therefore there is no point to search for *Toxocara* eggs in human feces [12,14].

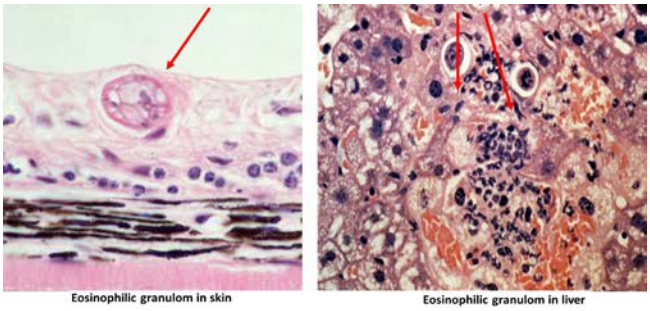

Figure 1. Pathological view

Antibody response against Toxocara antigens can reach a measurable level within four days and four weeks and may remain in the serum for years. The most important disadvantage of serological tests is the possibility to observe crossreactions in many parasitary infections such as *Ascaris*, *Strongyloides*, *Fasciola* and filarial nematodes [25]. Therefore, today we mostly prefer to use enzyme-linked immunosorbent test (ELISA) where *T.canis* excretory secretory (TES) antigens are used and western blotting test (WB) in the serological diagnosis of toxocariasis. Many researchers reported that ELISA where TES antigens are used and WB methods are quite sensitive and specific in the serological diagnosis of *Toxocara* infections in human beings [13,25].

Routine ophthalmological examinations are important for the diagnosis of OLM. The larva is rarely observed during the microscopic evaluation of the anterior chamber of the eyeball (Figure 2). The presence of antibody can be searched for diagnosis in serum and eye fluid.

However, it was reported that serum antibody levels may be low or negative in ocular infections and that the test may result positive if a test is carried out by obtaining intraocular fluid from the patient [12,14].

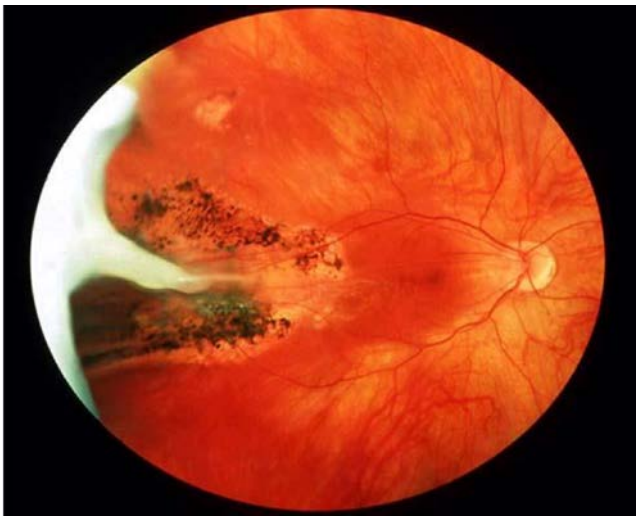

Figure 2. Ocular Larva Migrans

Differential Diagnosis

It is necessary to carry out a differential diagnosis for toxocariasis from other parasitic diseases that display same clinical symptoms and a similar invasion. The following diseases should be considered: ascariasis, fasciolasis, strongyloidiasis, anklyostomiasis, filariasis and schistosomiasis. It is also recommended to perform a differential diagnosis from diseases that may show high eosinophilia such as chronic eosinophilic leukemia, Hodgkin's disease, familial hypereosinophilia and hypereosinophilia induced by drugs [26].

Treatment

Visceral toxocariasis may be treated with antiparasitic agents such as albendazole, thiabendazole or mebendazole. It is stated in medical literature that evaluation of the affectivity of antiparasitic therapy is difficult for toxocariasis. In asymptomatic forms of the disease, the efficacy of treatment may be marked by clinical symptoms disappearance, however it is not always correlated with concomitant decrease in serological infection markers. In asymptomatic forms of the disease, the detection of specific anti-*Toxocara* IgG does not appear to be useful for monitoring therapy, as positive titers seem to be present over a long period of time. According to Bass et al., when ELISA antibody titers were compared between treated and untreated children, they did not differ significantly as a result of antiparasitic treatment [27]. Wisniewska-Ligier et al. demonstrated that if high titers of specific antibodies were still detected 6 months after treatment, with presence of eosinophilia and/or other clinical symptoms of toxocariasis, antihelmintic treatment was repeated [28].

Treatment of ocular toxocariasis is more difficult and usually consists of measures to prevent progressive damage to the eye. Ocular involvement sometimes needs surgical treatment.

Prognosis

A small number of larvae usually forms infections in toxocariasis and therefore the prognosis of this condition can be considered as *good*. Even in patients who demonstrate symptoms, the condition is typically considered benign and may disappear without leaving a sequel. However, it is reported that serious complications and even death can occur due to the migration of the larvae into vital organs such as the eyes, brain or heart. Some children may also experience loss of vision, epilepsy and temporal hemiparesis [29].

Protection

It is very simple to protective yourselves from toxocariasis by taking effective precautions, however it is also important to know that the environment must be cleared from *Toxocara* eggs and children must be prevented to contact with such eggs. Cats and dogs must be regularly controlled for the presence of *Toxocara* and other parasites and treated with antiparasitic drugs while stray animals must be taken under control and soil-eating habits in certain areas prevented [30,31]. It is easy to combat against Toxocariasis due to the administration of anthelmintic drugs which helps a lot to eliminate mature parasites from the intestines of dogs and cats [32].

As a result, we should not forget that parasitary infections are frequently seen in environments where hand hygiene is poor whereas the condition may lead to different clinical symptoms. In daily work, *Toxocara* infections could be underestimated and should be kept in mind that toxocariasis may be present in areas where dogs and cats are large in number; furthermore, a differential diagnosis must be considered in the diagnosis of *canis toxocariasis* in patients whom referred to clinics due to eosinophilia.

Especially, it is essential to remember to periodically administer anthelminthic drugs to kittens and puppies younger than six months which may reduce the possibility of an infection.

Conflict of Interest statement

We have no competing interests to declare.

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