TOXOCARIASIS - WHAT DO WE KNOW? A LITERATURE REVIEW

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ABSTRACT

Toxocariasis is a helminthic zoonosis caused by the presence and migration of animal nematode larvae in human tissue – mostly *Toxocara canis* and *Toxocara cati*. The term visceral larva migrans syndrome was used for the first time in 1952 by Beaver et al. who described the typical clinical presentation. There are difficulties in the diagnosis of toxocariasis because of the variety of symptoms depending on the larva localisation in different tissues and organs. Currently, the most commonly used serological methods are ELISA and Western blot. The disease is characterised by diverse clinical picture and thus toxocariasis is very rarely identified and most patients remain undiagnosed, which requires in-depth study of this widespread but still problematic zoonosis.

KEYWORDS:

Toxocariasis, diagnosis, VLM, OLM

HISTORY OF HUMAN TOXOCARIASIS

The nematode parasites *Toxocara canis* and *Toxocara cati* were described for the first time by Werner in 1782 who initially named the dog parasite *Lumbricus canis,* and Schrank in 1788 naming the cat parasite *Ascaris cati*. In 1947 Perlingiero and György reported the first case of toxocariasis in 2-year-old boy presenting with typical symptoms – liver involvement, anaemia and fever (1). Two years later, in 1949, Zuelzer and Apt investigated 8 similar cases and described the syndrome observed in young children and characterised by pica, pulmonary involvement with fever, enlarged liver, eosinophilic granuloma, chronic blood eosinophilia, anaemia and hyperglobulinaemia (2). The aetiology of the disease was still unknown until Mercer et al. discovered in 1950 the aetiological agent – ascarid larvae in liver biopsy samples from a child with specific syndrome manifestation (3). Human toxocariasis was first described in 1950 by Wilder C. when he discovered the nematode larvae and their residual hyaline capsules and published a report on ocular granuloma in patients with endophthalmitis (4). The larva was identified later in 1956 by Nichols who performed histological examination of Wilder's samples and determined it as *Toxocara* spp. (5). Two years later, in 1952, Beaver et al. described the clinical manifestation of the disease in children characterised by significant chronic eosinophilia, hepatomegaly, lung infiltrates, fever, cough, hyperglobulinaemia and presence of second-stage larvae of *T. canis* in liver biopsy samples (6). The authors established the term “visceral larva migrans” (VLM) referring to the migration of the larvae through tissues of infected persons and the clinical symptoms caused by their presence in tissues and organs (6). Three decades later Taylor et al. defined the third syndrome of human toxocariasis – covert toxocariasis with non-specific symptoms and signs, associated with increased levels of anti-*Toxocara* antibodies and observed in cases which are not categorised as ocular larva migrans (OLM) or classic VLM syndrome (7).

AETIOLOGY

The causative agents of toxocariasis are classified in kingdom Animalia, phylum Nematoda, class Secernentea, order Ascaridida, superfamily Ascaridoidea, family Toxocaridae, genus *Toxocara*, species

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Toxocara canis (Werner, 1782) and *Toxocara cati* (Schrank, 1788). The family Toxocaridae includes 21 species but the most important causative agents of human disease are *T. canis* and *T. cati*. The intestinal parasite in cattle and buffaloes – *T. vitulorum* (Goeze, 1782) is believed to infect children in the tropics, and *T. pteropodis* (Baylis, 1936), a fruit bat nematode, is considered the causative agent of hepatitis outbreak in Australia. Two new species were recently identified – *T. malayasiensis* (8) in domestic cats and *T. lyncus* (9) in wildcats, but their zoonotic potential is not yet proven. *Toxocara canis* and *T. cati* are ascarid nematodes whose adult forms inhabit the intestinal lumen of dogs, cats and wild carnivores. They are large roundworms with size of 6-18cm for *T. canis* female species and 4-10cm for male species. The size of *T. cati* nematodes is 4-12cm for female and 3-6cm for male species (10). The infectious larvae of *T. canis* and *T.cati* are 400μm long and 15-21μm in diameter. These two species are almost morphologically identical but the diameter of the larva of *T. cati* is smaller (*T. canis* – 18-21μm, *T. cati* – 15-17μm). The eggs of the two species are undistinguishable under light microscopy – they are almost spherical, with thick, rough shell and black granular content. The eggs of *T. canis* (75x90μm) are sometimes larger than those of *T. cati* (65x75μm) (11).

LIFE CYCLE

Definitive hosts and source of infection are dogs, cats, foxes, coyotes etc., spreading the parasite's eggs in the external environment. The adult parasites live inside the host for about 4 months and after that they are eliminated spontaneously. Female forms produce more than 200 000 eggs which can remain vital in the soil for a long period of time. The eggs are unembryonated and non-infectious when they are excreted. Special conditions of the environment are required for embryonation. In optimal conditions, such as temperature between 25-30^{o}C and humidity of 85-95%, the larval stage development inside the egg takes 9-15 days (12). During the incubation period the larvae transform from first-stage to second-stage larvae. The duration of the development may vary from 3-6 weeks to several months and the infectious stage may remain viable inside the egg up to 1 year (13). The endurance of *Toxocara* egg coat makes it highly resistant to many disinfectants and only extremely high temperature, dryness and sunlight can kill the parasite. The infection of dogs and cats occurs through ingestion of eggs, larvae transmission from the mother to her offspring or through ingestion of a paratenic host. After ingestion of the eggs the second-stage larvae hatch in the host's intestines, migrate via the liver to the heart and lungs and again enter the gut where the parasite reaches sexual maturity (tracheal migration). Some of the larvae reach the lungs and disseminate to different organs and tissues through the blood vessels (somatic migration) without any further development (hypobiosis). Actually, in older dogs and cats the parasite does not complete its life cycle and the larvae encyst in tissues while migrating throughout the body. The life cycle is usually completed in females and their offspring and larval reactivation occurs only in pregnant or lactating cats and dogs. In pregnant dogs larvae could be activated under hormonal stimulation and transmitted to the foetus transplacentally (14), and therefore newborn dogs are often infected. Transplacental transmission is not observed in cats and the primary infection of kittens is through transmammary transmission which is less significant in dogs (15). In paratenic hosts, larvae encysted in the intestine following ingestion, penetrate the mucosa and migrate to the organs (lungs, liver, eyes, brain) but cannot develop to adult forms and encyst in the tissues. These larvae are potentially infectious to the host's predators. When a cat or dog ingests the infected paratenic host, the larvae complete their development in the intestinal tract after being released from the tissues during the digestive process (10). This transmission type is called

paratenesis. Rodents, lambs, pigs and birds could be *Toxocara* paratenic hosts.

Humans can also be paratenic hosts. Infection occurs after ingestion of eggs from dirty hands, soil, food, water, contact with infected animal or ingestion of larvae after consumption of uncooked meat from domestic paratenic animals. Infection may also ensue after consumption of raw or uncooked chicken, pork, beef or lamb organs containing larvae (16). Different invertebrates such as flies, cockroaches (17) and earthworms (18) can be mechanical carriers of *Toxocara* spp. Toxocariasis is a zoonosis and there is no data on human-to-human direct transmission. Galactogenic transmission of *T. canis* is not mentioned in the literature.

TOXOCARIASIS IN HUMANS

After ingestion of embryonated *Toxocara* eggs, second-stage larvae hatch in the intestines, enter the blood and lymphatic systems from where they reach different organs. In the tissues larvae encapsulate and become surrounded by eosinophilic granulomas. They cause persistent infections and different pathological and clinical disorders. The larvae can remain viable in human tissues for one or more years. Inactive larvae can be reactivated anytime and start to migrate (19). The disease pathology is mainly a result of tissue damage caused by inflammatory response to the presence of larvae and the toxic products they produce. The larvae do not grow in tissues but they are metabolically active and secrete huge amount of enzymes, waste products and cuticle components which cause tissue damage, necrosis and significant inflammatory reaction. Eosinophilia is the main manifestation of this reaction (20) and it is considered that eosinophils produce toxic proteins contributing to toxocariasis pathology and symptomatology (21). *Toxocara* larvae products have high immunogenicity and allergenicity which explains the rate of allergic symptoms in patients with toxocariasis (22). The larvae are found in liver, lungs, heart, eyes and brain (23) where they form migratory tracks characterised by haemorrhage, necrosis and inflammation. The inflammatory response in the eye may lead to partial or total retinal damage with loss of vision (24). Pathology is related to the death of the larva which triggers the development of early or late manifestation of hypersensitivity (25).

Clinical forms of the disease

The ingestion of *Toxocara* larvae by humans may not lead to development of disease or could cause systemic illness affecting different organs. In the literature, systemic toxocariasis is observed in 15.5% of all diagnosed cases and most of the infections caused by *Toxocara* spp. are asymptomatic (26). The severity of the disease depends on the affected tissue, the number of migrated larvae, the immune response and age of the host (25). Due to its variety of symptoms and signs, toxocariasis is divided into three main forms – visceral, ocular and covert (7). According to a newly suggested classification, human toxocariasis is classified in one of the following forms – classical systemic form, asymptomatic, covert and compartmentalised (ocular and neurological). The last two forms are deemed as separate because the eyes and brain are the target organs of larvae migration (27).

Visceral larva migrans (VLM)

Symptoms of classical systemic VLM include periods of fever, cough, wheezing, anaemia, eosinophilia, hepatomegaly and positive serological tests. Eosinophilia up to 30% or more is considered significant for the clinical diagnosis in children with a history of eating soil (28). The clinical picture progresses mainly to leucocytosis (29, 30), eosinophilia (6, 31), lung and liver dysfunction, neurological disorders. Lung symptoms caused by larvae invasion are observed at the beginning of the disease. These symptoms may be preceded by eosinophilia and hepatomegaly and could be accompanied by fever. Iron-deficiency anaemia is commonly observed. There is also a considerable increase in isohemagglutinin

titres due to antigenic similarity between parasites and human erythrocytes (32). Lung involvement is associated with cough, dyspnoea, infiltrates and mimics bronchitis or pneumonia (33) with eosinophilic pleural effusions (34) and acute (35) or chronic eosinophilic pneumonia (36). When liver is affected the condition usually progresses to granulomatous hepatitis (37). Heart damage is observed rarely with myocarditis (23, 38) or pericarditis (39). Larvae can reach the brain where they cause neurotoxocariasis. The damage of the central nervous system (CNS) manifests as meningitis, encephalitis (40), myelitis (41) or cerebral vasculitis (42). Patients complain of headache, fever, light sensitivity, weakness, confusion, fatigue and visual disorders. Dementia, depression or behavioural disorders are also reported (43). It is considered that some types of epilepsy are related to brain lesions caused by larvae migration (44, 45, 46). Damage of the peripheral nervous system is rare presenting as radiculitis (47), cranial nerve damage or musculoskeletal dysfunction (48). Toxocariasis may be associated with some less common manifestations, such as generalised lymphadenopathy (49) and idiopathic urticaria (50). Some authors (51) reported occurrence of asthma in patients with toxocariasis and described a correlation between the two diseases (52). It can be concluded that VLM damages many organ systems and the clinical presentation can mimic a lot of diseases (53). The syndrome is usually benign, self-limiting and the prognosis is favourable. Significant damages to lungs, liver, CNS and even a fatal outcome could occur if there is delay in diagnosis and treatment.

Ocular larva migrans (OLM)

Conditions in which the visual system is affected are called ocular larva migrans. *Toxocara* larvae have affinity for the retina and their migration through the tissues causes haemorrhage, necrosis, ocular inflammation and lesions which often lead to loss of vision in the infected eye (54). The inflammatory reaction against larvae and their antigens can cause local or general damage of the retina or other eye structures. Usually, the infection is unilateral and most common in children but sometimes both eyes could be involved. Typical features of ocular toxocariasis include nematode endophthalmitis (4), retinal granuloma (55, 56), reduced vision, leukocoria, red eye and strabismus (57). Often there is no eosinophilia (58) and the diagnosis is usually based on the presence of chorioretinal granuloma, focal lesions in the posterior ocular segment and positive serology. According to the literature, the distribution of OLM is from 0% to 10% (59).

Covert toxocariasis is characterised by non-specific signs and symptoms which are not classified in the classic VLM, OLM or neurological toxocariasis (NLM). The term is introduced by Taylor who described the most common clinical characteristics – stomach ache, hepatomegaly, anorexia, nausea, vomiting, sleep and behaviour disorders, pneumonia, cough, rales, pharyngitis, cervical adenitis and limb pain (7). Lung involvement (asthma, acute bronchitis, pneumonia) (60), skin problems such as chronic urticaria or eczema (61), lymphadenopathy, myositis, pseudorheumatoid syndrome (62) are also observed. Covert toxocariasis is often diagnosed when the symptoms disappear after treatment (19).

Asymptomatic toxocariasis has no symptoms and diagnosis is based only on positive serological test. It is observed as minor or old infections and could be accompanied by eosinophilia (63). The main problem with this form, especially in children, is the risk of progression to OLM or NLM. Bass et al. reported 7% to 44.4% distribution of asymptomatic toxocariasis (63).

Diagnosis of human toxocariasis

Parasitological diagnosis of toxocariasis is difficult because the parasite does not reach sexual maturity or produce eggs. The only way to make a precise diagnosis is based on

observation of the larvae in biopsy tissues (4, 5). However, identification is extremely difficult due to their small size and the procedure posing a risk to the patient. Typical changes in the tissues are the formation of eosinophilic abscess and granuloma with fibrinoid necrosis and larva in the centre often surrounded by thick hyaline capsule. Liver biopsy is performed in patients with VLM. Motile larva can be directly observed below the retina in the ocular form (64). Therefore, immunology methods determining the presence of specific IgG antibodies against the parasite's antigens are the main instruments in the diagnosis of toxocariasis. In 1979 de Savigny developed ELISA methodology based on *T. canis* antigen obtained from *in vitro* cultivation of second-stage larvae, and reported that the assay is sensitive for diagnosis of toxocariasis (65). Later on, researchers confirmed the method and described it as sensitive, specific and easy to perform (66). Nowadays, this is the most commonly used screening tool for diagnosis and sero-epidemic investigations. Cross-reactions (66), difficult interpretation of borderline results and low sensitivity in cases of ocular form are often reported as disadvantages of the method (67). In order to avoid these drawbacks, in 1991 Magnaval et al. developed Western blot assay (68) using excretory-secretory antigens of *Toxocara* larvae. The presence of toxocariasis is associated with formation of a first cluster of low-molecular-weight bands (LMW) of 24, 28, 30 and 35 kDa and a second cluster consisting of three high-molecular-weight bands (HMW) of 132, 147 and 200 kDa, which are observed more often in examination of patients with different helminthiases. According to Magnaval, the Western blot method correlates with ELISA and he suggested to be used as a confirmatory tool of all positive ELISA results (68). Because of the good sensitivity and specificity, nowadays the Western blot method is recognised as a confirmative test for *Toxocara* serology (69).

Immunological reactions of intraocular liquids (aqueous and vitreous humour) (70) are recommended in OLM diagnosis and significantly increase the specificity of ELISA, but such specimens are usually not available for examination.

Serodiagnostic tests have few disadvantages. The occurrence of cross-reactions with other parasites (most often with nematodes) often shows false positive reactions. The stage of disease and treatment success cannot be determined because of the long retention time of specific antibodies (71). Difficulties in the diagnosis of *T. canis* active infection are serious problem and for this reason additional tests are further developed – measurement of circulating antigens (72), determination of total serum IgE level (73, 74, 75) and eosinophil cationic protein (ECP) (76, 77). Other complementary tests include determination of specific IgG avidity (78), anti-*Toxocara* IgE (79) and specific IgG subclass antibodies (80, 81), in order to support the main diagnosis and determine the activity of the disease.

Lesions caused by larvae can be identified with different medical imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) (82, 83, 84).

Genetic methods (PCR) are used for detection of ascarid larvae in animal tissues (cats, dogs and foxes) and species differentiation between *T. canis*, *T. cati* and *T. leonine* (85). Reliable genetic markers for identification and differentiation of *Toxocara* species and related nematodes are the first and second internal transcribed spacers (ITS-1 and ITS-2) of the nuclear rDNA sequence (85, 86, 87). In 2013, Pinelli E. determined *Toxocara* spp. DNA in bronchoalveolar lavage fluid of experimentally infected mice and suggested this method for improving the diagnosis, especially in patients with lung symptoms (88). Mitochondrial genetic markers (mDNA) are used for investigation of *Toxocara* spp. taxonomy and population genetics (89). The main focus of genetic studies is on *T. canis* and the identification of dominant and surface molecules secreted during the infectious larva stage, which have a key role in the immune

invasion (90). The application of modern genetic and bioinformation technologies is of great importance for understanding the biology of *T. canis* and will lead to development of new diagnostic, therapeutic and control strategies (91).

Toxocariasis in Bulgaria

In our country R. Zheleva investigated *T. canis* antigen structure and contributed to the development of different diagnostic techniques (92). I. Raynova performed extensive studies of the disease incidence in Bulgaria and standardisation of modern serological tests (ELISA and Western blot) (93).

Toxocariasis is one of the most widespread helminthic infections in the world. Investigation of the distribution in Western countries reveals 2% to 5% in healthy residents of cities, 14% to 37% in adults living in the countryside (94) and up to 63% in the tropical countries (95). Studies in Bulgaria show 8.6% distribution in healthy people (96). There are several reasons for the high levels of soil contamination with *Toxocara* eggs, such as the wide spread and fertility of adult *Toxocara* spp. parasites and increase in the number of pet animals. Geography and poor personal hygiene increase the risk of *Toxocara* infection, especially in children. Due to difficulties in diagnosis and the variety of clinical forms, the disease often remains undiagnosed. The increase in awareness of this illness will lead to early diagnosis and proper treatment.

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