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REVIEW

Human Toxocariasis: 2010 to 2020 Contributions from Brazilian Researchers

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Abstract: This is a review of the published contributions made by Brazilian researchers between 2010 and 2020 on the natural history of human toxocariasis and the effects of human toxocariasis on nonhuman paratenic hosts.

Keywords: *Toxocara*, *Toxocara canis*, toxocariasis, visceral larva migrans syndrome, Brazilian contribution

Introduction

Human toxocariasis, first described in 1952 by Beaver et al,[1] is currently considered an important zoonosis and the main cause of visceral larva migrans (VLM) and other syndromes, such as ocular larva migrans (OLM), covert toxocariasis (CT), and neurological toxocariasis.[2–5] Signs and symptoms of the main clinical types of human toxocariasis are[6–8]

Visceral Larva Migrans – fever, pallor, malaise, irritability, weight loss, cutaneous rash, hepatomegaly, respiratory and nervous disturbs, myocarditis, hypergammaglobulinemia, leukocytosis and eosinophilia, elevated anti-A and anti-B isohemagglutinins; Ocular Larva Migrans – visual loss, strabismus, retinal granuloma and detachment, endophthalmitis, chorioretinitis, uveitis; Covert Toxocariasis – coughing, abdominal pain, headache, sleep and behavioral disturbances.

An analysis of the published toxocariasis research from 1932 to 2015 showed that researchers from the United States of America and Japan were responsible for 18.5% of a total of 2765 papers identified in the Scopus database, followed by researchers from Brazil and the United Kingdom, each responsible for 6.5% of the published papers.[9]

In 2009, Chieffi et al[10] published a paper reviewing the contributions of Brazilian researchers to the main aspects of the natural history of human toxocariasis. The aim of this current paper is to update the Brazilian contributions on the natural history from 2010 to 2020. The MEDLINE and LILACS databases were used and representative articles consisting of papers published by Brazilian researchers were selected.

Toxocara canis Infection in Dogs and Soil Contamination by *Toxocara* Eggs

Dogs and other canids are the natural hosts of *Toxocara canis*; they can be infected via several routes; however, the transplacental and transmammary migration of third-

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stage larva are the principal mechanisms leading to the maintenance of high levels of infection in young dogs.[11] Under certain conditions, *T. canis* can infect cats and develop into adult worms. Additionally, *T. cati* can infect dogs.[12] In humans, with few exceptions, *Toxocara* infections lead to the presence and migration of larvae, which remain in the third developmental stage.

Stray dogs are usually controlled in the urban areas of Brazil; however, control does not necessarily extend to many suburban or rural localities, where stray dogs are not dewormed, which thus negatively impacts public health.

The most important route for human infection is the accidental ingestion of the embryonated eggs of *Toxocara*. The prevalence of *T. canis* infections in dogs, therefore, as reflected by soil contaminated by ascarid eggs, should be considered a good index of the risk of human infection by *Toxocara* larvae. Chieffi et al[10] previously referred to parasitological soil surveys conducted in several Brazilian locations, which showed huge variations in the rates of *T. canis* infections in dogs, ranging from 5.5% to 39%.

Some publications from 2010 to 2020 by Brazilian researchers reported on the rates of *T. canis* infection in dogs and confirmed the rates that had already been established.[13–15] However, a serological investigation in Salvador (Bahia State) revealed that 82.7% of 301 dogs were positive for anti-*Toxocara* IgG antibodies.[16] On the other hand, Merigueti et al[17] examined 165 dogs at a veterinary hospital and found *T. canis* eggs in 6.7% of samples of dog hair that were mainly collected in or near the dog tail.

Several Brazilian researchers investigated the soils of public spaces for *Toxocara* eggs between 2010 and 2020 (Table 1) and almost always found high positivity rates.[18–25] Santarém et al[19] found higher numbers of *Toxocara* eggs in the soil of public parks with mean monthly temperatures and monthly amounts of rainfall. Queiroz et al[26] had also noticed increased soil contamination at a similar time.

Frequency and Characteristics of Human Infections Due to *Toxocara*

Researchers aiming to assess the frequency of human *Toxocara* infections in Brazil began to emerge in the late 1980s. The main serological surveys carrying out this aim up to 2009 have been summarized elsewhere.[10] Tables 2 and 3 summarize the rates of infection in adults and in children. The tables reveal broad variations in infection rates, but highlight the importance of the morbidity of *Toxocara* infections in humans, especially children, and mainly is those aged from 1 to 8 years.[27]

It is important to note, however, the scarcity of surveys based on samples that are statistically representative of the population being investigated, which perhaps accounts for the varying rates that have been sometimes found in the same regions or from areas nearby.

Figures 1 and 2 show the geographical location in Brazil of positive tests for anti*Toxocara* antibodies in adults and children, examined by ELISA.

In Rio Grande in Southern Brazil, 8% of 200 pregnant women were found to be coinfected with *Toxocara canis* and *Toxoplasma gondii*. This coinfection was associated with neonates with low birth weights.[48,49]

Frequent contact with soil or with dogs and cats has been identified as a risk for human *Toxocara* infection, especially in children.[18,29,31,33,36,40] According to Colli et al,[27] contact with the soils of recreational areas of schools is a higher risk of *Toxocara* infection in children than frequent contact with the soils of public squares.

Mattos et al[50] performed an interesting study that determined the prevalence of infection and risk factors of infection in researchers who worked frequently with *Toxocara* in the laboratory. The control group consisted of researchers without contact with *Toxocara* in their laboratory activities. They found that the group working with *Toxocara* showed a lower frequency of infection compared to the controls (13.8% vs 15.6%, respectively), indicating that the *Toxocara* researchers, possibly because they were taking special precautions, were less exposed to the risk of *Toxocara* infection than the controls.

Changes in liver and pulmonary parameters are frequent in human toxocariasis, mainly in children. Although less frequent, ocular and brain lesions and allergic manifestations can occur.[51] Carvalho et al[52] used abdominal ultrasound to reveal hepatic changes such as hypoechoic liver lesions and/or enlarged lymph nodes in 29.7% of 37 children with toxocariasis.

The relevance of allergic manifestations in patients with toxocariasis is controversial among Brazilian researchers. Zaia et al[53] observed acute allergic inflammation of the airways of mice infected by *T. canis*. Silva et al[54] reported a patient with Loeffler syndrome who had been infected by *T. canis*. The patient only showed marked improvement after treatment with thiabendazole. On the other hand, Grama et al[55] and Cadore et al[56] did not find an association between atopy and an increased

Table 1 Soil Contamination by *Toxocara* Eggs in Public Places in Brazilian Locations, from 2010 to 2020

Authors	Local	n	Method	Positivity (%)
Manini et al (2012)[18]	Maringá (Paraná State)	15	Water-sedmentation	100*
Santarém et al (2012)[19]	Presidente Prudente (São Paulo State)	25	Centrifuge-flotation	96.0
Marques et al (2012)[20]	Guarulhos (São Paulo State)	47	Spontaneous-flotation	74.5
Ribeiro et al (2013)[21]	Belo Horizonte (Minas Gerais State)	42	Spontaneous-flotation	42.4
Sprenger et al (2014)[22]	Curitiba (Paraná State)	69	Centrifuge-flotation	9.6
Capella et al (2018)[23]	Pelotas (Rio Grande do Sul State)	100	Spontaneous-flotation	3.0
Mello et al (2019)[24]	Pelotas (Rio Grande do Sul State)	79	Spontaneoussedimentation	11.9
Leon et al (2020)[25]	Laguna dos Patos (Rio Grande do Sul State)	6	Centrifuge-flotation	8.3

Note: (*) 100% of public squares, 18.9% of peridomicile, 23.1% in schools.

risk of asthmatic manifestations in children with serological tests positive for anti-*Toxocara* antibodies. In 2012, Mendonça et al[51] did not find an association between positivity for aeroallergens and *Toxocara* infections in children living in poor areas of Salvador (Bahia State) and postulated that increased polyclonal IgE levels and the induction of a modified Th2 immune response to *Toxocara* infection might prevent the development of skin hypersensitivity to aeroallergens. On the other hand, Fialho and Corrêa[57] found an association between asthma and increased body mass index in children and adolescents living in Campinas (São Paulo State), and Fialho et al[58,59] confirmed a positive association between urticaria and infection with *Toxocara* in children.

Recuero et al[60] described a case of eosinophilic panniculitis as a rare skin manifestation associated with

Table 2 Percentage of Human Seropositivity by *Toxocara* in Adults in Some Brazilian Regions

Authors, Year	Location	N	Frequency (%)
Colli et al (2010)[27]	Maringá (Paraná State)	376	51.6
Dattoli et al (2011)[28]	Salvador (Bahia State)	306	46.3*
Souza et al (2011)[29]	Salvador (Bahia State)	338	52.0
Prestes-Carneiro et al (2013)[30]	Pontal do Paranapanema (São Paulo State)	194	14.4
Negri et al (2013)[31]	Presidente Prudente (São Paulo State)	253	8.7
Santos et al (2015)[32]	Rio Grande (Rio Grande do Sul State)	280	6.4+
Pereira et al (2016)[33]	Brasília (DF)	311	7.4+
Araújo et al (2018)[34]	Rural population of Rio Grande do Sul State	344	71.8

Note: (*) Blood donors (+) pregnant women.

Table 3 Percentage of Human Seropositivity by *Toxocara* in Children in Some Brazilian Regions, Tested by ELISA

Authors, Year	Local	N	Frequency (%)
Correa and Bismarck (2010)[35]	Campinas (São Paulo State)	100	28.0
Santarém et al (2011)[36]	Presidente Prudente (São Paulo State)	252	11.1
Fragoso et al (2011)[37]	Vitória (Espírito Santo State)	391	51.6
Marchioro et al (2011)[38]	Maringá (Paraná State)	1199	32.2
Mattia et al (2012)[39]	Maringá (Paraná State)	353	36.8
Manini et al (2012)[18]	Maringá (Paraná State)	90	17.8
Mendonça et al (2013)[40]	Salvador (Bahia State)	1309	48.4
Guilherme et al (2013)[41]	Maringá (Paraná State)	167	4.2
Schoenardie et al (2013)[42]	Rio Grande (Rio Grande do Sul State)	427	50.6
Oliart-Guzmán et al (2014)[43]	Assis Brasil (Acre State)	421	12.3
Cassenote et al (2014)[44]	Rio Preto (São Paulo State)	252	15.5
Marchioro et al (2015)[45]	Maringá (Paraná State)	544	25.0
Silva et al (2017)[46]	São Francisco do Conde (Bahia State)	791	63.6
Araújo et al (2020)[47]	Rio Grande (Rio Grande do Sul State)	41	43.9

Figure 1 Geographical distribution in Brazil of anti-*Toxocara* antibodies in adults examined by ELISA from 2010 to 2020.

toxocariasis in a 5-year-old girl with an ELISA positive for *Toxocara*. Albendazole treatment (10 mg/kg/day for 10 days) provided complete resolution of her condition. Another uncommon complication of toxocariasis in a child was reported by Salvador et al,[61] who described the concomitant involvement of the cerebrum, cerebellum, and the peripheral nervous system of a 5-year-old boy from Porto Alegre (Rio Grande do Sul State).

Acute joint manifestations are common in toxocariasis; however, chronic polyarthritis as an isolated manifestation is very uncommon. Viola et al[62] reported the case of a 3-year-old girl with chronic severe, painful polyarthritis and 30 min of morning stiffness that lasted longer than 10 weeks. The patient was positive for anti-*Toxocara* antibodies on ELISA. Treatment with paracetamol and thiabendazole for 10 days led to reduction in all the clinical manifestations of the infection.

Laboratory Diagnosis of Human Toxocariasis and Toxocariasis in Other Paratenic Hosts

Parasitologists usually prefer to diagnose parasitic infections by demonstrating the presence of the parasite in the host organism. The diagnosis of human toxocariasis is only possible through a biopsy, which is both extremely invasive and is sometimes neither safe nor accurate. The use of immunohistochemical techniques, in turn, allows identification of *Toxocara* antigen expression in

Figure 2 Geographical distribution in Brazil of anti-*Toxocara* antibodies in children examined by ELISA from 2010 to 2020.

histological sections.[63] However, because biopsies are invasive, they are not common, and indirect diagnostic techniques are therefore more common.

Traditional indirect laboratory methods employed for the diagnosis of human toxocariasis rely usually on enzyme-linked immunosorbent assays (ELISAs) and Western blots. However, the production of *T. canis* antigens for use in those evaluations is arduous and time-consuming, taking at least 60 days,[64] and does not eliminate possible cross-reactions with other similar antigens of other intestinal parasites.[65] Several Brazilian researchers tried to resolve the shortcomings of the methods used in the diagnosis of human toxocariasis during the period from 2010 to 2020.

In an attempt to improve the sensitivity and specificity of immunological tests for the diagnosis of human toxocariasis, several researchers sought to identify possible markers of infections and the immunodominant antigens of *T. canis*.[64,66–70]

Roldán et al[71] showed that IgM antibodies used for the serodiagnosis of human toxocariasis showed low specificity, and Santos et al[72] found that *Toxocara* recombinant antigens developed with the use of the yeast *Pichia pastoris* instead of *Escherichia coli* showed low sensitivity for the immunodiagnosis of *Toxocara* infections. On the other hand, when Santos et al[73] previously used recombinant antigens of low molecular weight (30 kDa), they obtained better results, especially in surveys that included children.

Some researchers have dedicated themselves to the study of the somatic and surface proteins of *T. canis*. They have obtained results that, in addition to contributing to the improvement of immunological tests, have provided information that allows the development of potential vaccines.[74,75]

The laboratory diagnosis of human ocular toxocariasis represents a greater challenge than the diagnosis of the visceral form because the levels of serum antibodies in the host are usually low and sometimes undetectable.[76,77] Imaging modalities such as ultrasonography or optical coherence tomography should be useful additions to the clinical examination of patients suspected to have ocular toxocariasis.[78,79] However, if ocular toxocariasis is suspected, despite the risks, an assessment of specimens of the aqueous or vitreous humor is recommended.

Aspects of the immune response of nonhuman paratenic hosts, with possible benefits for surveys aimed at determining the frequency of infections by *Toxocara* larvae, have been studied in vivo, in mouse or rabbit models.[80–90] Serological surveys carried out on synanthropic animals that are paratenic hosts of *T. canis* revealed significant natural frequencies of infection, indicating that there is a risk involved in the human consumption of raw or undercooked meat from these animals.[91–94] Recombinant proteins used in ELISAs and Western blot assays for the diagnosis of *Toxocara* infections of cattle, horses, and sheep have obtained good results.[95]

Treatment and Prophylaxis of Human Toxocariasis

Although the anthelminthic treatment of dogs with patent intestinal infections of *T. canis* shows good results; the anthelminthic treatment of *Toxocara* larvae encysted in canine tissues has been ineffective.[6] In human toxocariasis, ascarid larvae migrate or encyst in tissues; thus, the use of various anthelmintics such as diethylcarbamazine and benznidazole derivatives has not led to the complete elimination of encysted larvae but has usually reduced or controlled the symptoms of those infections.[96]

Some Brazilian researchers also have tested anthelmintics in rodents infected by *T. canis*. Lescano et al[97] compared the effect of nitazoxanide, a drug recently used for the treatment of several human protozoal and helminthic infections, with mebendazole, a benznidazole derivative known to reduce the *Toxocara* larval load in experimental rodent infections. They found a greater reduction in the number of larvae in the rodents treated with mebendazole than in those treated with nitazoxanide.

Another group of researchers tested the effects of quinone derivatives against *Toxocara* larvae in vitro, as well as their anthelmintic action in experimental rodent infections.[98,99] They found good in vitro larvicidal activity and an anthelmintic activity similar to that found with benznidazole derivatives. Sinott et al,[100] in turn, reported that the essential oil extracted from Brazilian red propolis showed good *Toxocara* larvicidal activity. On the other hand, Avila et al[101] showed an increase in the larval burden of *Toxocara* in mice treated with cyclophosphamide or dexamethasone, drugs commonly used in immunosuppressive treatments.

Probiotics have recently been studied by some researchers, including researchers in Brazil, as possible alternatives for the control or even treatment of human toxocariasis.[64] Avila et al[102] found a significant reduction in the burden of *Toxocara* larvae in mice that were treated with *Saccharomyces boulardii* for 15 days. However, in a subsequent in vitro experiment they noticed a lack of action by *S. boulardii* on *T. canis* larvae in vitro, indicating that an interaction with the intestinal mucosa is mandatory for the protective effect of *S. boulardii*.[103] The same researchers postulated that this type of protection could be provided through the modulation of cytokine expression, especially IL-12[104,105] Walcher et al[106] found that the probiotic *Lactobacillus rhamnosus* showed protective results similar to those provided by *S. boulardii*.

Another line of investigation, which is focused on the prophylaxis of toxocariasis, is the possible deleterious effects of some fungi on *Toxocara* eggs. Thus, the in vitro studies of the fungus *Pochonia chlamydosporia* showed its deleterious effects on *T. canis* and *T. vitulorum* eggs.[107–109] Other species of fungi in the *Trichoderma* and *Fusarium* genera also showed deleterious in vitro activity against *Toxocara* eggs.[110,111]

Verocai et al[112] showed that *Toxocara* eggs were resistant to solutions of sodium hypochlorite, benzalkonium chloride, and formaldehyde-based disinfectants. However, 70% ethanol led to the complete degeneration of *Toxocara* eggs in a few days.

Some researchers have focused on the use of synanthropic animals such as chickens as sentinels for soil contaminated by *Toxocara* eggs.[113,114]

Experimental Studies in Nonhuman Paratenic Hosts

Several researchers have focused on the roles and importance of the vertical and transmammary transmission of *T. canis*. Schoenardie et al[41] verified the vertical transmission of *T. canis* in mice either with chronic infections or infections during the acute phase. The importance of the transmammary route in the transmission of *T. canis* in mice was emphasized by a group of researchers from the Federal University of Rio Grande, in the state of Rio Grande do Sul.[115,116]

The migration patterns of *T. canis* were studied in experimental infections of mice and gerbils. In *Rattus norvegicus*, a significant difference was found between the migration patterns according to the sex of the animals. Female rats showed a greater number of larvae in the liver than males.[117] Resende et al[82] studied the immunopathology of T. canis infections in mice and found similar larval migration patterns, with innate induction of TH17/TH2 responses during early infection. The migration patterns of *T. canis* larvae in the gerbil *Meriones unguiculatus* were similar to the patterns already observed in mice and rats; however, in reinfected animals, more larvae were apparently retained within hepatic granulomas, without evident signs of destruction.[118]

There are numerous references in the literature on behavioral changes in rodents experimentally infected with *T. canis*, which are associated with larvae located in the central nervous system.[119,120] Before reaching the nervous system, the larvae pass through muscle tissues, being able to determine alterations.[7] Santos et al[121] observed a decrease in the strength of the muscles of rats (*R. norvegicus*) infected with *T. canis* or *T. cati*. The reduction in muscle strength was greater in rats infected with *T. cati* than in rats infected with *T. canis*. Researchers from the same group[26,122] studied the patterns of behavioral changes in mice and rats concomitantly infected with *T. canis* and *Toxoplasma gondii* and observed that the obvious changes that occurred in animals infected with *T. canis* only or *T. gondii* only were not manifested in mice and rats with concomitant infections of both parasites.

The hamster (*Mesocricetus auratus*) is another species of rodent that is frequently used in the laboratory. It has been characterized by histopathological, immunohistochemical, and immunoelectron microscopic findings as a good animal model for research on toxocariasis.[123]

Conclusions

Evidence on the occurrence of human toxocariasis in Brazil indicates that additional well designed and comprehensive epidemiological studies are needed. The studies should be applied to the entire nation in order to understand the spatial distribution of this zoonosis and provide reliable information for implementing a national program to control it.

Disclosure

The authors report no conflicts of interest in this work.

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