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# Review Article

# Toxocariasis in humans: clinical expression and treatment dilemma

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**Abstract**

A new scheme of clarifying clinical forms of toxocariasis is proposed to include: (i) systemic forms: classical VLM and incomplete VLM; (ii) compartmentalized forms: ocular and neurological toxocariasis; (iii) covert toxocariasis; and (iv) asymptomatic toxocariasis. The following markers are helpful in defining clinical forms namely, patient characteristics and history, clinical symptoms and signs, positive serology, eosinophilia and increased levels of IgE. Amongst the available drugs albendazole is the most commonly used, although other benzimidazole compounds have a similar efficacy. The recommended dose of albendazole is 15 mg $kg^{-1}$ body weight daily for 5 days and in some cases with VLM syndrome the treatment needs to be repeated. An evaluation of treatment efficacy can be made by observing a rise in eosinophilia within a week followed by any improvement in clinical symptoms and signs, lower eosinophilia and serological tests taken over a period of at least 4 weeks. In addition to clinical rationales for the specific treatment of VLM and OLM, preventive treatment needs to be considered bearing in mind the increasing risk of larvae localizing in the brain during the course of an infection. To reduce migration of *Toxocara* larvae a single course of albendazole is suggested in cases where eosinophilia and serology are at least moderately positive.

## Introduction

Toxocariasis, as measured by positive serological tests, is common in humans. In population studies the range of seropositivity varies between 2 and 80% (Thompson *et al.*, 1986). Although high titres of positive tests are observed mainly in children, the seropositivity, irrespective of titres, may even be higher in the adult population (Glickman *et al.*, 1987; Łużna-Lyskov *et al.*, 2000). The role of the intensity of seropositive responses is discussed below as one of the important points in the clinical judgement of toxocariasis.

The spectrum of clinical manifestations in toxocariasis varies widely from asymptomatic cases, most commonly occurring, to severe organ injury, e.g. an eye (Taylor *et al.*, 1988). The manifestation and clinical course are determined by the size of the inoculum, frequency of reinfections, localization of *Toxocara* larvae and the host response. The size of the inoculum and frequency of reinfections cannot be measured in humans, but infections are assumed to be frequent in environments heavily contaminated with *Toxocara* eggs or in children with geophagia. Localization of larvae may be identified by clinical examination, when the eye or brain are involved and by imaging techniques, as in the case of detecting liver granulomas.

Except for mechanical injury caused by migrating larvae, e.g. in the eye or brain, an immunopathogenic mechanism mainly underlines clinical manifestations of toxocariasis (Kayes, 1997). Such a mechanism is mediated in various proportions by Th1 cells (a granuloma formation, considered to be a delayed-type of hypersensitivity) and Th2 cells (an increase of IgE

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antibodies and eosinophils) (Kayes, 1997). IgE-dependent eosinophil-mediated helminthic toxicity may occur in humans but this has not been observed in mice, which is one of the most common experimental models for toxocariasis (Jones *et al.*, 1994). Various allergic, atopic and eosinophil-related injuries largely depend upon the type of individual response within a *Toxocara* infected host.

In such a situation, it is often difficult to take a rational decision on the eventual specific treatment of toxocariasis, which is frequently a self-limiting and asymptomatic infection. Such a decision might be easier after considering: (i) the clinical presentation of toxocariasis in humans; (ii) markers of various clinical forms of toxocariasis; and (iii) anthelmintic availability and treatment efficacy which are considered in the present paper to provide a rationale for the specific treatment of toxocariasis. The paper is originally presented at the VIII European Multicolloquium of Parasitology held Poznań, Poland in September 2000.

## Clinical presentation of human toxocariasis

Several clinical forms of human toxocariasis have been described but few attempts make a general and complete classification of observed clinical expressions of *Toxocara* infections (Bass *et al.*, 1983; Gillespie, 1993; Magnaval *et al.*, 1994; Petithory *et al.*, 1994); An older French classification into major and minor forms of toxocariasis, although useful for didactic purposes, seems to be a simplification of the presentation of varied clinical expressions of *Toxocara* infections (Magnaval, 1987). The most recent classification considers the active and regressing infections, but by categorizing cases simply as either symptomatic or asymptomatic discords with the wide spectrum of specific and non-specific symptoms and signs occuring in human toxocariasis (Magnaval *et al.*, 2000). The proposed new general classification is a compromise between an observed clinical status, the involvement of immunopathologic mechanisms, including the intensity of the serological response, and the location of *Toxocara* larvae. The present classification divides human toxocariasis into four major forms namely: systemic, compartmentalized, covert and asymptomatic (table 1).

The classic visceral larva migrans syndrome (VLM), described by Beaver *et al.* (1952), is a severe systemic form of toxocariasis, characterized by high eosinophilia, hepatosplenomegaly, fever, hypergammaglobulinaemia and pulmonary involvement. Cases of VLM, which is a severe clinical condition, are uncommon and occur almost entirely in small children. Among the possible consequences of prolonged and extensive eosinophilia are pulmonary fibrosis (Phan & Kunkel, 1992) and eosinophilic myocardosis (Friedman & Hervada, 1960; Dao & Virmani, 1986; Kendell *et al.*, 1995; Hokibara *et al.*, 1998). More common is an incomplete visceral larva migrans syndrome (iVLM), proposed by Łużna-Lyskov *et al.* (2000) which is restricted to clinically much less severe cases, in which only some signs of the classic VLM form may occur, e.g. hepatomegaly and high eosinophilia.

There are two main compartmentalized forms of toxocariasis: ocular toxocariasis (OLM) and neurological toxocariasis (NLM – which is the term being proposed). Both forms should be classified separately from other forms on the basis that a specific organ, i.e. the eye or brain, is likely to be the final site of *Toxocara* larval migration. There is an extensive literature on ocular toxocariasis, which may be more readily observed than cephalic toxocariasis. However, there is no reason that the brain is less commonly invaded than the eye but involvement of the brain in parasitic invasions is frequently asymptomatic and remains undiagnosed, e.g. in neurocysticerciasis. It has been hypothesized that ocular toxocariasis occurs in infections with low invasive doses whereby insufficient stimuli for a protective immune response create no limits to the migration of *Toxocara* larvae. On the other hand, in infections with high doses of invasive larvae the filtering effect of the liver becomes overwhelmed and the number of *Toxocara* larvae migrating to other organs is likely to be considerable (Glickman & Schantz, 1981). In the brain, *Toxocara* larvae are not encapsulated and the tracks of their migration usually comprise small areas of necrosis and a minimal inflammatory infiltration (Hotez, 1993). There-

Table 1. Classification of the clinical forms of human toxocariasis and justification for clinical and 'preventive' treatments.

| | Clinical characteristics | | | | | Justification for treatment | |
|---|---|---|---|---|---|---|---|
| Clinical forms | Patient characteristics | Symptoms and signs | Serology | Eosinophilia | Specific IgE | Clinical | Preventive[a] |
| Systemic | | | | | | | |
| Classic VLM | XXX | XX | XXX | XXX | XX | yes[b] | |
| Incomplete VLM | X | X | XX | XX | X | yes | yes[c] |
| Compartmentalized | | | | | | | |
| OLM | XXX | XXX | X | ? | ? | yes | |
| NLM | X | X | X | ? | ? | yes | |
| Covert toxocariasis | ? | X | XX | ? | XX | yes | yes[c] |
| Asymptomatic toxocariasis | 0 | 0 | X | ? | ? | no | to be considered[c] |

NLM, neurological larva migrans; OLM, ocular larva migrans; VLM, visceral larva migrans syndrome.
Intensity of clinical characteristics expressed as: XXX, strong; XX, moderate; X, weak; ?, doubtful; 0, none.
[a] One course of albendazole 15 mg $kg^{-1}$ b.w. (400, 600 or 800 mg daily) × 5 days.
[b] In some cases treatment needs to be repeated.
[c] If serology is moderately positive (OD > 1200) and eosinophilia > $400 \times 10^9\, l^{-1}$.

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fore, in NLM several cases are asymptomatic whereas in the other cases the symptomatology may vary widely. A case-control study in humans infected with *Toxocara* concluded that the migration of larvae in the human brain does not frequently induce recognizable neurological symptoms or signs (Magnaval *et al.*, 1997). However, symptoms such as subtle neurological deficits, focal or generalized seizures, behavioural disorders and eosinophilic meningoencephalitis have been reported in individual human cases of toxocariasis (Hill *et al.*, 1985; Cox & Holland, 1998). Knowledge of experimental infections in mice indicate that the proportion of *Toxocara* larvae localized in the human brain may increase over the course of infection (Wade & Georgi, 1987; Skerrett & Holland, 1997; Helwigh *et al.*, 1999) and a low local immunological response is expected to remain high for a long time (Dunsmore *et al.*, 1983).

Covert toxocariasis, the term introduced by Taylor *et al.* (1987), is less well defined and frequently undiagnosed but it can commonly occur (Kincekova *et al.*, 1999; Łużna-Lyskov *et al.*, 2000). By definition, covert toxocariasis is characterized by non-specific symptoms and signs, which do not fall into the categories of classic VLM, incomplete VLM, OLM or NLM. Covert toxocariasis seems to depend less on a local reaction to *Toxocara* larvae but is more an organ oriented immunopathological host response to continued stimulation of the host immune system by parasite antigens. In different individuals predisposed organs may also differ so that in covert toxocariasis clinical expression varies widely and may present as a pulmonary involvement such as asthma, acute bronchitis, pulmonitis with or without a Loeffler syndrome (Buijs *et al.*, 1995; 1997; Feldman & Parker, 1992), dermatological disorders such as chronic urticaria or eczema (Wolfrom *et al.*, 1995), lymphadenopathy, myositis and a pseudorheumatic syndrome such as arthralgia (le Lauyer *et al.*, 1990; Kraus *et al.*, 1995). Analysis of the causal relation of *Toxocara* infection with clinically observed symptomatology requires a good clinical knowledge and a proper evaluation of clinical tests including IgG and IgE specific antibodies, eosinophilia and hypergammaglobulinaemia. However, covert toxocariasis is often only confirmed by alleviation or disappearance of non-specific symptoms and signs after specific anti-*Toxocara* treatment.

Asymptomatic toxocariasis, diagnosed by positive serology, occurs mainly in light or old infections, and may be accompanied by eosinophilia but most frequently is not (Bass *et al.*, 1983, 1987). It should be noted that dormant *Toxocara* larvae may be reactivated any time and migrate again.

## Markers of various clinical forms of toxocariasis

A definitive diagnosis of toxocariasis in humans can only be made by locating the larvae either by biopsy or autopsy. All other indirect methods suggest that a *Toxocara* infection may be responsible for a disease present in a particular patient. There are five major markers of symptomatic toxocariasis: (i) the characteristics and history of the patient; (ii) clinical symptoms and signs, (iii) positive serology, (iv) eosinophilia and (v) increased levels of the IgE class of immunoglobulins.

The age of a patient may indicate an increased risk of having clinically expressed toxocariasis. Classic visceral larva migrans syndrome (VLM) is most frequent in children below the age of 5 years. The clinical presentation of OLM has been observed to be age dependent: diffuse toxocaral endophthalmitis occurs most frequently in the age category of patients between 2 and 9 years, retinal granuloma between 6 and 14 years and pars planitis between 6 and 40 years (Vegh & Danka, 1987). Patient sex, on the other hand does not appear to be an important factor in the frequency of toxocariasis in human populations. The most reliable factor linked with clinical toxocariasis is geophagia, which occurs mainly in children under 5 years of age. Contact with an infected dog, especially puppies, is generally accepted to be a risk factor for toxocariasis, whereas inhabiting rural areas, once believed to be a major risk factor, is now less important, as toxocariasis has been observed more frequently in the urban environment (Fok & Rozgonyi, 1999; Łużna-Lyskov, 2000).

With reference to clinical symptoms and signs, VLM syndrome can be expressed clinically in a varied intensity. A classical form of VLM syndrome can easily be suspected clinically but an incomplete VLM syndrome or less evident cases of OLM frequently create problems of diagnosis. A suspicion of covert toxocariasis is likely to be a second or third option in seropositive cases presenting non-specific symptoms and signs.

Positive serology is a most important marker of *Toxocara* infections in humans and encompasses all clinical spectra of toxocariasis from asymptomatic to severe forms. However, positive serology does not necessarily indicate a causative relationship between *Toxocara* infection and a patient's current disease. Serology using an enzyme immunoassay with excretory/secretory (E/S) antigens has a sensitivity of 80% and a specificity of 90–95%, which is even higher in immunoblot assays (Jacquier *et al.*, 1991; Magnaval & Baixench, 1993). False positive results may occur in strongyloidiasis, trichinelliasis and fascioliasis. False negative results are rare and only occur in some localized early or very old infections (OLM). The intensity of a serological test, measured either by a titre, an index or an optical density (OD), is likely to be correlated with the intensity of *Toxocara* infection and its activity and clinical expression. In our experience, cases with an OD $< 1.200$ are rarely symptomatic and reflect a very high rate of light or old *Toxocara* infections in the population. An OD value of 1.800 in practice is accepted as the borderline between asymptomatic and symptomatic infections (Łużna-Lyskov *et al.*, 2000). However, children living in highly contaminated areas have OD values close to 1.800 and remain asymptomatic (Łużna-Lyskov, 2000). Classic VLM has an OD value of over 2.000, whereas patients with OLM have low OD values, but these observations need to be confirmed using other ELISA assays. However, if the intensity of serological responses are not analysed, it would be difficult to evaluate the public health and clinical importance of toxocariasis in areas where seropositivity is common in the human population.

Eosinophilia measured in the peripheral blood is proportional to tissue eosinophilia, which is a local reaction to *Toxocara* larvae or antigens remaining in the

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tissue following larval migration. Eosinophils constitute a major component of cellular infiltrations or granulomata. The role of eosinophils in killing *Toxocara* larvae is less clear than in other parasitoses, probably due to an extended period of invasion and also the development of specific evasion mechanisms by the *Toxocara* larve against eosinophil attack (Meeusen & Balic, 2000). Eosinophilia occurring in seropositive *Toxocara* cases reflects the activity of the pathological process and as such plays an important role in deciding subsequent treatment. Usually the intensity of eosinophilia corresponds to the intensity of infection and also the serological response (Łużna-Lyskov *et al.*, 2000). In our experience, eosinophilia is neither present in 73% of patients with covert toxocariasis, nor in 9% of those with incomplete VLM syndrome nor 81% of cases suspected for OLM (Łużna-Lyskov *et al.*, 2000). Theoretically the lack of eosinophilia occurs in old or very light infections. The intensity of eosinophilia, measured by the chamber technique, is also of some diagnostic value. In our experience eosinophilia of $400–1000 \times 10^9 l^{-1}$ is most common in asymptomatic cases, covert toxocariasis and incomplete VLM syndrome whereas eosinophilia above $3000 \times 10^9 l^{-1}$ is typical of classic VLM cases.

Among the 933 patients with eosinophilia in the Clinic of Parasitic and Tropical Diseases in Poznan, Poland, 16% showed positive *Toxocara* serology. On the other hand, among 136 patients with positive toxocaral serology, 58 patients (42.6%) had eosinophilia. A high leucocytosis usually runs parallel with high eosinophilia but because there are frequently several other reasons for increased leucocytosis in clinical practice, leucocytosis is not considered to be a good marker for clinical toxocariasis (Łużna-Lyskov *et al.*, 2000).

*Toxocara* IgE antibodies are present in some cases of human toxocariasis (54%) and are highly specific (Żarnowska *et al.*, 1995). The total IgE level is usually proportional to the level of specific toxocaral IgE antibodies but is less specific. According to Obwaller *et al.* (1998) toxocaral specific IgE antibody levels are higher in symptomatic (35%) than in asymptomatic (24%) cases. There is a highly significant correlation between the formation of IgE/anti-IgE human complexes and the clinical course of toxocariasis as a disease (Obwaller *et al.*, 1998). A specific IgE level is usually proportional to a specific IgG antibody level. However, Obwaller *et al.* (1996) and Magnaval *et al.* (1992b) have shown that the intensity of eosinophilia is a better marker that the level of IgE antibodies for the evaluation of treatment. On the contrary in patients with cutaneous signs of allergy, related to toxocariasis, high total IgE levels are more frequent than eosinophilia (Magnaval, 1987).

In summary, the ranking of existing 'markers' of toxocaral disease (except VLM and OLM) is as follows: clinical symptoms and signs, confirmed by positive serology and eosinophilia, in a patient at risk of infection, with or without an increased specific IgE level.

## Anthelmintic availability and treatment efficacy

There are two groups of anthelmintics used in the treatment of human toxocariasis, namely older drugs, such as diethylcarbamazine and thiabendazole, and newer compounds of the benzimidazole group such as albendazole, fenbendazole and mebendazole. Experimental data on the efficacy of ivermectin in toxocariasis are still insufficient. Diethylcarbamazine, effective against various filarial larvae can be administered twice daily for 3 weeks in increasing doses from 1 to 3 mg $kg^{-1}$ body weight (b.w.). Diethylcarbamazine therapy is long known to provoke allergic reactions, although it is accepted as one of the most effective in the treatment of toxocariasis (Wiseman *et al.*, 1971; WHO, 1995). Thiabendazole has been used for a number of years at a dose of up to 50 mg $kg^{-1}$ b.w. for 3 to 5 days, but the drug has been withdrawn from wider use due to its poor tolerability and potential side effects (Aur *et al.*, 1971; WHO, 1995). Among the benzimidazole drugs, albendazole is more frequently used than mebendazole (Stürchler *et al.*, 1989; Magnaval *et al.*, 1992a; Magnaval, 1995). We use albendazole at 15 mg $kg^{-1}$ b.w. for 5 days, but the efficacy of this regime has, to date, not been assessed vs. placebo nor vs. another drug such as thiabendazole or diethylcarbamazine.

It should be noted that a comparison of drug efficacy in humans is difficult as groups treated by various authors vary widely in the degree of *Toxocara* infection, clinical expression and methods of evaluation of successful treatments. Considering the available literature and our own clinical experience, the following ranking of drug efficacy is proposed, namely, diethylcarbamazine > thiabendazole > benzimidazole compounds (albendazole, fenbendazole, mebendazole) with some reservation that diethylcarbamazine and thiabendazole are now currently not in frequent use due to the need for prolonged therapy or due to their poor tolerability.

It must be emphasized that although the use of an anthelmintic reduces the number of *Toxocara* larvae, it may have less or no immediate effect on allergic reactions related to toxocariasis. On the contrary, during or shortly after treatment, allergic or atopic conditions may result in a rise in the levels of detectable antibodies and eosinophilia (Cuellar *et al.*, 1990; Magnaval *et al.*, 1992a), indicating that some larvae have been destroyed and an additional amount of antigen released. In practice it would be useful to compare the level of eosinophilia prior to, during and a week after anthelmintic treatment. However, it is unlikely that all migrating or dormant larvae are killed but, in cases which improve clinically after treatment, one may expect that a substantial portion of *Toxocara* larvae have been destroyed. Experiments using mice demonstrated that albendazole therapy may kill up to 40% of *Toxocara* larvae in the brain and up to 10% in the musculature and the results are improved if treatment is given earlier (Abo-Shehada & Herbert, 1984; Delgado *et al.*, 1989). However, these observations in mice may not have much practical application as human infections are usually diagnosed at a later stage. New approaches to the treatment for toxocariasis through the use of immunomodulators and liposomes have recently been reviewed by Dubinsky (1999).

## Rationale for specific treatment of toxocariasis

Classic and incomplete VLM syndromes and covert toxocariasis may require non-specific, symptomatic

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treatment because of concomitant pathological processes, such as pulmonitis, spastic bronchitis, asthma, urticaria and anaemia, but this is not discussed in the present paper. Similarly, the treatment of ocular toxocariasis, which depends much on individual cases, is left to ophthalmologists to consider.

Some authors question the need for the treatment of *Toxocara* infections by indicating that toxocariasis is a self-limiting condition (Mikulecky & Mikulecky, 1994; Kazura, 1997). This is not a strong argument because human toxocariasis is a chronic infection, which may last for a number of years and reactivated larval migration into the eye or the brain may occur at any time.

There are two rationales for specific toxocaral treatment: (i) a clinical picture in a particular patient; and (ii) an attempt to reduce the number of *Toxocara* larvae potentially migrating into the brain or eye (table 1).

A clinical justification for specific treatment is obvious in cases with a VLM syndrome and some cases with an incomplete VLM syndrome or covert toxocariasis. Because of possible allergic adverse reactions there are no rules for specific treatment of symptomatic ocular toxocariasis nor neurological toxocariasis and what remains is the best clinical judgement in a particular case. Sometimes an antiallergic cover has to be given with an anthelmintic.

In some seropositive cases without any clinical expression of toxocariasis, an attempt to lower the number of dormant or migrating larvae by specific treatments has to be considered. A few markers related to the intensity of infection and to any active pathological process may be helpful in making such a decision. A high intensity of infection in patients is likely to be related to a high exposure to eggs of *Toxocara* plus high levels of serological responses and eosinophilia. The actual pathogenic activity of the parasite can be expected in cases with at least a medium intensity of serological responses ($OD > 1.200$) and eosinophilia in the range of $> 400 \times 10^9\,l^{-1}$. For such cases a preventive treatment comprising one course of albendazole at 15 mg $kg^{-1}$ for five days should be considered.

Reinfections in human toxocariasis, which are common in contaminated environments mainly via geophagia, have a definitive impact on the pathological process. It is therefore essential to educate any patient with toxocariasis, symptomatic or not, treated or not, on how the infection is acquired and the reasons why reinfections need to be avoided. The prevention of human toxocariasis is feasible and effective by: (i) the regular deworming dogs and cats beginning at 3 weeks of age, repeated three times at 2-week intervals and every 6 months thereafter; (ii) preventing contamination of the soil by dog and cat faeces in areas immediately adjacent to houses and children's playgrounds; (iii) the regular washing of hands after handling soil and before eating; (iv) taking care that children do not place dirty objects into their mouths and controlling geophagia (Benenson, 1995).

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