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ORIGINAL RESEARCH

Seroprevalence of IgG anti-Toxocara species antibodies in a population of patients with suspected allergy

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Background: *Toxocara canis* is an intestinal nematode affecting dogs and cats, which causes human infection when embryonated eggs excreted in dog feces are ingested. Humans are paratenic hosts. Although the larvae do not develop into adult worms in the human body, they may migrate to various tissues and organs where they can survive for several years, giving rise to several clinical symptoms, which can present in allergy-like form.

Methods: Over 5 years, we examined 9985 patients referred for suspected allergies, based on symptoms such as dermatitis, urticaria, rhinitis, asthma, and conjunctivitis; 753 patients who had allergy tests negative or unrelated to clinical history were tested for seropositivity to *T. canis* by enzyme-linked immunosorbent assay (ELISA) or Western blotting (WB).

Results: In 240 patients (31.8%), ELISA or WB or both tests were positive for *T. canis* immunoglobulin G (IgG) antibodies: in particular, 64 of them (26.7%) were positive to ELISA, 110 (45.8%) to WB, and 66 (27.5%) to both tests. Asthma was the most common clinical presentation. Two thirds of patients underwent subsequent anthelmintic therapy and showed a complete remission of symptoms and, in 43% of patients retested by ELISA and WB, became negative to *Toxocara*.

Conclusion: These findings strongly suggest that *T. canis* plays a significant role in inducing chronic symptoms presenting as suspected allergies.

Keywords: suspected allergy, *Toxocara canis*, enzyme-linked immunosorbent assay, Western blotting, anthelmintic therapy

Introduction

Allergic diseases in Western countries have steadily increased over the last 20 years, affecting the respiratory system, conjunctiva, and skin.[1,2] Moreover, an emergent aspect is the association of gastrointestinal involvement with respiratory and/or cutaneous symptoms, arising from allergies and/or intolerance. Gastroenteric expressions of these diseases include acute symptoms (diarrhea or vomiting) and chronic symptoms (bloating, constipation which may alternate with diarrhea). Allergy tests, performed with commercial extracts or fresh foods, can be negative or slightly positive in most patients in both situations.[3] Allergy tests may also be negative in respiratory and cutaneous allergy, and this enables a distinction between, eg, allergic and nonallergic asthma, allergic and nonallergic rhinitis, and allergic and nonallergic dermatitis.[4]

Different explanations for this increase in prevalence have been hypothesized, including genetic predisposition,[5,6] environmental factors,[7,8] or the "hygiene hypothesis",[9] but none of these possibilities seems to be completely satisfactory. In this context, since the role of immunoglobulin E (IgE) antibodies is central to the development of

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allergies, factors related to the onset of symptoms must also include the possibility of helmintic infections, which induce high IgE levels. The IgE increase is proportional to both the severity of infection and invasion of parasites in the tissues, and is the sum of the total IgE level plus parasite-specific IgE release.[10,11] The latter derives from helmintic production of factors that stimulate interleukin-4 production.[12] In particular, one study found an increase in circulating IgE levels during parasitic infections caused by Ascarids,[13] while other studies demonstrated a total IgE increase in parasitic diseases and their reduction after antiparasitic therapy,[14] as well as high IgE levels in patients affected by visceral larva migrans with antibodies against *Toxocara.*[15] The infestation caused by *Toxocara canis* appears to be very frequent in tropical countries, but also in some areas in Europe, especially among children in the first decade of life.[16,17] The symptoms caused by *Toxocara* infection in the different target organs in the respiratory, cutaneous, and gastrointestinal systems are often similar to the symptoms of allergic diseases. The aim of the present study was to evaluate the prevalence of seropositivity to *T. canis* in a large population of patients referred for symptoms of suspected allergy.

Methods and materials

Between 2003 and 2008, we evaluated 9985 new patients presenting with symptoms suggesting an allergic disease. The clinical symptoms involved seasonal or persistent rhinoconjunctivitis, asthma, urticaria, angioedema, and dermatitis.

All patients underwent clinical examination, careful evaluation of symptoms, and allergy tests, including skin prick tests with inhaled or food allergen extracts and, in patients with dermatitis, patch tests with a standard panel of haptens (Merck, Milan, Italy). Skin prick tests were performed with the panel of allergen extracts from Stallergenes, Milan, Italy.

Routine and immunological blood tests and parasitological tests on feces were performed, as well as symptomatic therapy, environmental prophylaxis as preventive treatment, an exclusion diet when food allergy was suspected, and replacement of medication(s) when a drug allergy was suspected.

A subgroup comprising 753 patients was selected who suffered from chronic recurrent respiratory, eye, skin or gastrointestinal symptoms caused by nonallergic mechanisms, as assessed by results to allergy tests negative or unrelated to clinical history, and these patients underwent further hematochemical and immunological blood tests, ie, enzyme-linked immunosorbent assay (ELISA), measured in optical density (OD) with a range from 0.9 to 1.1, and Western blotting (WB) tests for IgG antibodies to *T. canis,* using material from LTBio Diagnostics, Lyon, France. The results of WB were interpreted as shown in Figure 1. These patients mainly suffered from asthma, urticaria, dermatitis, and conjunctivitis; less frequently they suffered from gastroenteric symptoms, asthenia, headache, dizziness, or drug reactions. The prevalence of the different clinical presentations was compared using the Chi-squared test.

Anthelmintic therapy was prescribed for *T. canis* seropositive patients, using mebendazole (one 100 mg tablet twice daily for 3 days, 5 mL syrup twice daily in children), repeated after 20 days up to three times in an effort to achieve significant symptomatic improvement. In the event of lack of improvement, albendazole (one 400 mg tablet twice daily for 5 days in adults, 5 mg/kg divided in two half doses in children) was used, and repeated after two months. Drugs for symptomatic therapy were also prescribed. These were mainly antihistamines or topical steroids for rhinitis symptoms, inhaled beta-agonists and corticosteroids for asthma symptoms, antihistamines, and topical or systemic corticosteroids for skin symptoms, including

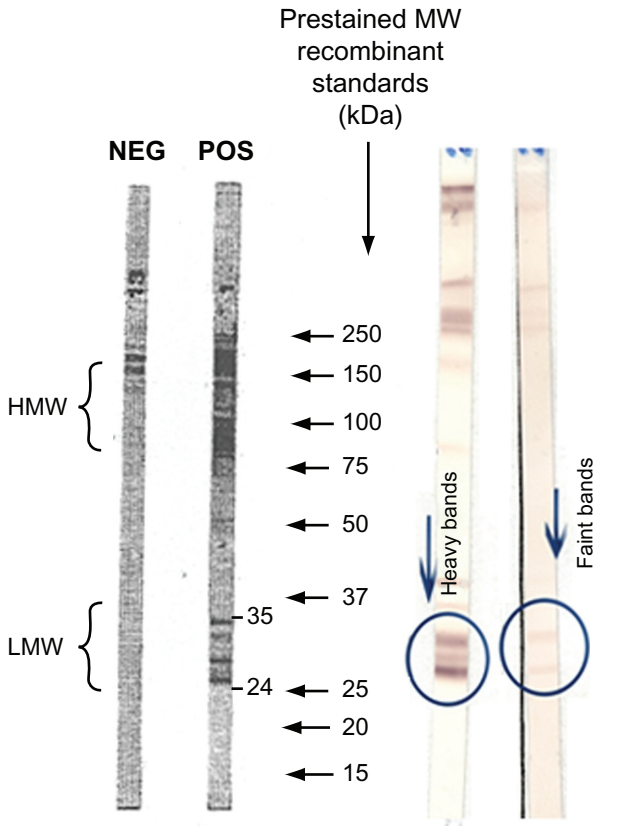

Figure 1 Western blot-specific IgG anti-*Toxocara canis*. Low molecular weight zone is *Toxocara*-specific. The presence on the strip of two or more low molecular weight bands in the range of 24–35 kDa is indicative of the presence of specific anti-*Toxocara* IgG in the sample.
Abbreviations: kDa, kiloDalton; NEG, negative; POS, positive; HMW, high molecular weight; LMW, low molecular weight.

urticaria/angioedema, dermatitis and itching, and probiotics (*Lactobacillus reuteri*) for intestinal symptoms. Regular control visits were scheduled, the first after 2 months and subsequently every 4 months. Patients who did not come back for the checkup visit were contacted by telephone about their symptoms. Clinical evaluations of symptoms and serological tests with the WB and ELISA for antibodies to *T. canis* were performed in patients who came to the visits. The study was registered (EudraCT number 2010-024221-20) and approved by local authorities. Informed consent was sought from all patients eligible for anthelmintic therapy.

Results

In the selected group of 753 patients suffering from chronic recurrent symptoms caused by nonallergic mechanisms, 240 (31.8%) tested positive for *T. canis* by ELISA, WB, or both tests; 64 of them (26.7%) were positive to ELISA, 110 (45.8%) to WB, and 66 (27.5%) to both tests. These patients included 222 adults (150 females, 72 males, age range 18–72 years) and 18 children (seven females, 11 males, age range 2–17 years).

Sixty-two of the 753 patients (25.8%) had animals at home (28 had a cat, 23 had a dog, and 11 had both animals). Fifty-two patients (23.3%) were atopic, with positive results to skin prick testing that were unrelated to clinical symptoms; in these patients, the mean level of total IgE was 280 kU/L. In the 188 nonatopic patients, the mean level of total IgE was 193 kU/L.

The clinical presentations of the patients are reported in Table 1. Asthma was significantly more frequent compared with the other presentations ($P = 0.029$ versus urticaria, $P = 0.002$ versus dermatitis, $P < 0.0001$ versus each other presentation). Among patients with asthma, five had level I, 30 had level II, 16 had level III, and eight patients had level IV disease according to the Global INitiative for Asthma (GINA) classification. Of the 240 *T. canis* seropositive patients, 162 (67.5%) agreed to undergo anthelmintic therapy, which resulted in considerable improvement in symptoms. Eighty-eight patients did not come for the checkup visit, but they were contacted by phone and confirmed that they did not suffer from symptoms any longer and did not use any more symptomatic drugs. In 14 of the 74 patients who came back to the scheduled control visits, we observed both clinical and serological improvement in WB and ELISA tests. In six of these patients, a decrease in the size of bands using WB was found; in five patients, the size of bands using WB and the OD using ELISA decreased, and ELISA OD values decreased from >1.1 to negative values in the range of 0.9–1.0 in three patients. There was a complete remission of symptoms with complete absence of antibodies to *T. canis* in 26 of the 74 patients. Table 2 shows the results of WB and ELISA.

Table 1 Clinical presentation of patients positive to *Toxocara canis*

Patients n (%)	Clinical presentation	Prevalence in selected population
59 (24.6)	Asthma	7.8%
36 (15)	Urticaria	4.8%
28 (11.7)	Dermatitis	3.7%
19 (7.9)	Conjunctivitis	2.5%
13 (5.4)	Colitis	1.7%
12 (5)	Headache	1.6%
12 (5)	Asthenia	1.6%
11 (4.6)	Cough	1.5%
10 (4.2)	Dysphagia/angioedema	1.3%
8 (3.3)	Itching	1.10%
7 (2.9)	Rhinitis	0.9%
15 (6.2)	Neurological symptoms (4 MS, 2 ataxia, 1 SLA, 3 ADHD, 5 epilepsy)	1.9%
10 (4.2)	Other symptoms	1.3%

Abbreviations: MS, multiple sclerosis; SLA, systemic lupus erythematosus; ADHD, attention deficit hyperactivity syndrome.

Discussion

Because we have previously observed cases of *T. canis* infection that simulated allergic manifestations and were mistakenly considered allergies for a long time,[18] we systematically tested allergic patients referred for suspected allergy (who had negative allergy tests or test results clearly unrelated to history) for seropositivity to *T. canis*. Of 753 patients with such characteristics, 240 (32%) were positive using in vitro tests (ELISA or WB) for IgG antibodies to *T. canis*. The role of *T. canis* infection in sustaining the symptoms was further demonstrated by the efficacy of anthelmintic treatment, which was evident in more than two thirds of treated patients and was associated with negativization or a decrease in *Toxocara* IgG antibodies in 43% of patients who underwent repeat ELISA or WB.

Human toxocariasis is a zoonosis sustained by parasitic infestation with the nematode *T. canis* belonging to the order of *Ascaris*, which infects dogs, cats, and many other mammals. A human host is occasionally infected via accidental ingestion of embryonated eggs in dirt. This happens mainly among children when they ingest soil while playing or eating. In human hosts, the larvae do not develop into adults, but they can migrate to different organs and tissues and survive for long periods of time, varying from a few months to decades, depending on the host immune response.[19]

The real incidence/prevalence of this infestation in humans has not yet been assessed, because the disease induces

Table 2 Changes in anti-*Toxocara* IgG antibodies as measured by ELISA and WB following anthelmintic treatment in clinically improved patients

Patient	Before treatment ELISA WB	After treatment ELISA WB
1	1.06 negative	<0.9 negative
2	>1.1 negative	<0.9 negative
3	>1.1 negative	<0.9 negative
4	1.04 negative	<0.9 negative
5	0.92 negative	<0.9 negative
6	>1.1 negative	<0.9 negative
7	1.00 negative	<0.9 negative
8	>1.1 negative	<0.9 negative
9	>1.1 negative	<0.9 negative
10	<0.9 faint bands	<0.9 negative
11	<0.9 faint bands	<0.9 negative
12	<0.9 faint bands	<0.9 negative
13	<0.9 faint bands	<0.9 negative
14	<0.9 faint bands	<0.9 negative
15	<0.9 faint bands	<0.9 negative
16	<0.9 faint bands	<0.9 negative
17	<0.9 faint bands	<0.9 negative
18	<0.9 faint bands	<0.9 negative
19	<0.9 faint bands	<0.9 negative
20	<0.9 faint bands	<0.9 negative
21	<0.9 heavy bands	<0.9 negative
22	<0.9 heavy bands	<0.9 negative
23	1.00 faint bands	<0.9 negative
24	>1.1 faint bands	<0.9 negative
25	>1.1 faint bands	<0.9 negative
26	>1.1 negative	<0.9 negative
27	>1.1 heavy bands	<0.9 faint bands
28	>1.1 heavy bands	1.08 heavy bands
29	<0.9 heavy bands	<0.9 faint bands
30	1.30 heavy bands	<0.9 faint bands
31	>1.1 heavy bands	0.99 heavy bands
32	>1.1 heavy bands	<0.9 faint bands
33	>1.1 heavy bands	>1.1 faint bands
34	>1.1 faint bands	0.99 negative
35	<0.9 heavy bands	<0.9 faint bands
36	1.00 faint bands	<0.9 faint bands
37	<0.9 heavy bands	<0.9 faint bands
38	>1.1 heavy bands	>1.1 faint bands
39	>1.1 heavy bands	<0.9 faint bands
40	>1.1 heavy bands	>1.1 negative

Abbreviations: ELISA, enzyme-linked immunosorbent assay; WB, Western blotting.

nonspecific symptoms. However, sometimes it mimics a viral infection, and in the mildest cases can be totally asymptomatic. Symptoms are classified based on three clinical outlines. The first one is called capsulated toxocariasis, which is characterized by very mild symptoms, with no clear clinical manifestations (for example, nonspecific illness with fever, recurrent hacking cough, insomnia, abdominal pain, headache, and behavioral disorders). The second one is called ocular larva migrans, limited to the eye, and may cause a reduction in sight, conjunctival hyperemia, recurrent conjunctivitis, and even granulomas, uveitis, and retinal detachment. The last one is visceral larva migrans, and its symptoms include fever, asthenia, behavioral depression (suggesting central nervous system involvement), skin afflictions like nodules, chronic hives, recurrent labial and eyelid angioedema and eczematous dermatitis, enteric symptoms such as meteorism and abdominal pain, respiratory symptoms such as dyspnea, persistent cough, recurrent asthmatic and bronchitic manifestations, pleuritis, and bronchopneumonia.[17,19]

Epidemiological studies conducted in Europe have shown variable prevalence of seropositivity for *T. canis*. In Spain, 14% of both pediatric and adult patients were found to suffer from eosinophilia, and 6% of these patients showed eye disorders.[20] In Sweden, the prevalence of seropositivity was about 7%, indicating a relevant presence of subclinical toxocariasis. In this group, eosinophilia was recognized in 32% of the sample, and the most common clinical manifestation was eye problems (46%) while neurological, respiratory and hepatic symptoms were described in 40% of these patients.[21]

In an Italian study that included 2112 healthy adult subjects, the prevalence of *T. canis* antibody seropositivity was 3.9%. The percentage increased in the control group of 471 nonhealthy subjects (257 affected by epilepsy, 142 by oligophrenia, 76 by *Strongyloides stercoralis* infestation), and was 4.35% in epilepsy patients, 9.2% in patients with strongyloidiasis, and 10.6%–14.5% in subjects with oligophrenia.[22] Thirty-one of 100 *Toxocara*-positive pediatric patients suffered from asthma or bronchitis, while the percentage decreased to only 12% among *Toxocara*-seronegative patients in a study performed in The Netherlands.[23]

Toxocara infestation mainly occurs via accidental ingestion of soil, that is why the illness usually affects children, but adults can also be infected. As stated above, the larvae do not develop in the human host but only migrate to different organs and tissues, where they survive for a certain time period depending on the level of the host immune response. Clinical manifestations can be nonspecific and difficult to recognize. They may even cause symptoms similar to viral infections or allergy-like symptoms, ie, may present with the clinical expression of allergy.

Symptoms can be mild, including fever, recurrent hacking cough, dyspnea, recurrent bronchitis, pleuritis, bronchopneumonia, asthma, skin afflictions like nodules and chronic hives, recurrent labial and eyelid angioedema and eczematous dermatitis, enteric symptoms, or even symptoms limited to the eye causing conjunctiva hyperemia and

recurrent conjunctivitis.[18,19] Most of these symptoms were present in the population we studied, in particular asthma, which was significantly more frequent than any other clinical presentation in patients with positive in vitro tests for *Toxocara*. This reinforces the suggestion made by Cooper that *T. canis* is an important and neglected environmental risk factor for asthma.[24] The role of *T. canis* infection may be assessed by the detection of specific IgG antibodies, it being known that the IgG4 subclass is predominantly involved in the response to parasitic infections.[25]

Conclusion

The findings from this study indicate that *T. canis* infection, as assessed by seropositivity of IgG antibodies by ELISA or WB, is not rare in patients presenting with symptoms of apparent allergy but with negative or inconclusive allergy tests. This suggests that serological tests should be performed to detect *Toxocara*-specific IgG antibodies in such patients and to assess the effect of anthelmintic treatment, in an effort to diagnose parasitic infection correctly in patients who are otherwise given a simple (but incorrect) diagnosis of nonallergic disease.

Disclosure

The authors report no conflicts of interest in this work.

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