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Toxocariasis associated with chronic cough in childhood: a longitudinal study in Hungary

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Abstract

Chronic cough lasting 8 weeks or more often seems to be an intractable problem in childhood. *Toxocara* infection is associated with an increased prevalence of airway symptoms and may be the possible aetiological agent of chronic cough. Of 425 children aged 2–17 years with chronic cough who were investigated for toxocariasis and the distribution of bronchial asthma (BA), cough variant asthma (CVA) and non-asthmatic eosinophilic bronchitis (NAEB), 136 (32%) were seropositive for *Toxocara canis* antigens. Ninety-three of the 136 were adequately assessed, diagnosed and followed up during 1 year. BA was diagnosed in 40%, CVA in 27% and NAEB in 33% of the children. The eosinophil cell count, serum *T. canis* IgG levels and symptoms are predictors of the improvement or the decline of the condition. Presuming the aetiopathogenetic role of *T. canis* in the inflammatory process of chronic cough, we treated the children not only with inhaled corticosteroid (ICS), but also with a 1-week course of anthelminthics. We could significantly decrease the dose of ICS in 23 (62%) of the 37 with BA. The administration of anthelminthics and the avoidance of sensitizers were sufficient for those with NAEB; none needed ICS. ICS therapy could be stopped 2–3 months later in 17 (68%) of the 25 with CVA. We found that 8 of the 25 with CVA (32%) presented asthmatic symptoms at the end of the 1-year period. In Hungary, *T. canis* may be a potential sensitizer for chronic cough in seropositive children. Deworming therapy will then alleviate the airway symptoms without exacerbation in patients with BA, and have a positive effect on those with NAEB and the majority of those with CVA.

Introduction

Chronic cough lasting 8 weeks or more is often seen as an intractable problem in childhood (Irwin *et al.*, 2006). One of the most common causes of chronic cough is bronchial asthma (Dicpinigaitis, 2006). The prevalence of bronchial asthma has increased during the past 20–30 years in developed countries, but there is a considerably lower prevalence in developing countries (Cookson & Moffatt, 1997). There are numerous environmental risk factors, such as pollution, increased exposure to allergens, changes in eating habits, and a decreased intake of antioxidants, which can account for atopic disorders, including bronchial asthma (Britton *et al.*, 1994; Hill *et al.*, 1997; Soutar *et al.*, 1997; Vormann, 2006).

There are two newly recognized entities in the background of chronic cough: cough variant asthma (CVA) and non-asthmatic eosinophilic bronchitis (NAEB). The prevalence of CVA varies by race and geographically, occurring more frequently in Asia than in Europe (Todokoro *et al.*, 2003; Lai *et al.*, 2006). It may be the precursor of bronchial asthma in almost 30% of cases

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(Fujimura *et al.*, 2005). The diagnosis of CVA is based on chronic cough without wheezing, with a normal chest X-ray and normal spirometry, but with bronchial hyperresponsiveness (BHR) to non-specific agents such as methacholine and histamine, and cough relief with the use of bronchodilator drugs (Irwin *et al.*, 2006). Patients with eosinophilic bronchitis have a bronchodilator-resistant chronic cough in 13% of cases (Brightling *et al.*, 1999), a normal lung function, atopy and no BHR to methacholine (Dicpinigaitis, 2006).

Atopy can be characterized by an elevated IgE level, and increased numbers of eosinophilic cells produced in the inflammatory process, resulting from stimulation of the Th2-dependent immune response (Holt *et al.*, 1999).

Toxocara infection is associated with an increased prevalence of airway symptoms and may be a possible aetiological agent of asthma (Buijs *et al.*, 1994). *Toxocara canis* is a nematode, a euryxenic parasite which can infect humans and canines and whose life cycle is based on transmission between animals. The frequency of *Toxocara* seropositivity in children with bronchial asthma varies between 6 and 68% (Oteifa *et al.*, 1998; Minvielle *et al.*, 1999; Zacharasiewicz *et al.*, 2000; Chan *et al.*, 2001).

The presence of migrating larvae in the paratenic host contributes to the pathology, depending on the site of the larvae and the intensity of infection (Kerr-Muir, 1994; Magnaval *et al.*, 2001). Allergic diseases are common in childhood, but their causes, in most cases, remain unknown.

The aim of the present study was to examine the potential role of *T. canis* infection in our outpatients with chronic cough.

Materials and methods

Four hundred and twenty-five consecutive and unrelated outpatients aged from 2 to 17 years who attended the Department of Pediatrics between January 2000 and September 2006 with a chronic cough (lasting 8 weeks or more) were enrolled into this study. In all cases, skin prick tests (SPTs), lung function and chest X-ray examinations were performed, and measurements were made of the peripheral blood eosinophil count, the serum total IgE level, and specific IgG antibodies against excretory and secretory (E/S) *T. canis* antigen at presentation.

Questionnaires for patients and their families

Detailed questionnaires were completed by the family, to ascertain the history of the child from the perinatal period, exposure to infections, the occurrence or not of smoking at home, risk factors for *T. canis* infection, the severity and nature of the cough, eating habits, the medication used, the character of the atopy, environmental factors and the family history.

Skin prick tests and lung function

Twelve common inhalative and 10 common nutritive allergens (Haarlems Allergens Laboratory, The Netherlands) were used in the SPTs, which were performed in each subject on the volar side of the forearm according to the guidelines of the Subcommittee on Skin Tests of the European Academy of Allergology & Clinical Immunology (1989).

Spirometry and bronchial reversibility tests were also performed. The latter were considered positive if the improvement in the forced expiratory volume in 1 second (FEV1) after the administration of 200 μg of a short-term β_2-agonist was $>15\%$. Non-specific bronchus provocation tests with a provocative dose of methacholine, histamine or adenosine and exercise producing a 20% decrease in FEV1 were carried out in patients who could cooperate in these tests (Global Initiative for Asthma, 1998).

Laboratory measurements

Blood eosinophil counts were measured with a haematologic analyser (Pentra 80 RAB108EA, ABX Horiba Diagnostics, Montpellier, France). The serum total IgE concentration was measured with ImmunoCAP™ Technology equipment (Pharmacia Diagnostics, Uppsala, Sweden). Results over 120 U ml^{-1} were considered to be elevated.

Toxocara canis serology

The serological examination for *T. canis*, based on the enzyme-linked immunosorbent assay of IgG (EIA *Toxocara canis* IgG, Test-Line, Clinical Diagnostics, Czech Republic; TLEIA) and more sensitive and specific Western blotting methods (*Toxocara* Western Blot IgG, LDBIO Diagnostics, France; LWB), was performed by the National Reference Laboratory for Helminthozoonoses at the National Center for Epidemiology in Budapest. The TLEIA was carried out according to the manufacturer's instructions. For the semiquantitative characterization of TLEIA results, the ratio method was used: the sample OD/cut-off ratio was multiplied by 10 and was rounded to the closest integer. With this index of positivity (IP), the sample is negative if IP is in the interval 0–8, borderline if IP is 9–11 and positive if IP ≥ 12. The LWB was carried out and interpreted in accordance with the manufacturer's instructions. The result was interpreted as positive if there were at least two visible bands on the strip in the range 24–35 kDa (Danka *et al.*, 2003).

The seroprevalences of symptomatic children were compared with those of 1605 asymptomatic children aged from 1 to 17 years, obtained in the frame of a national survey, especially from rural areas, where the presence of dogs, cats and other animals at home was more frequent than in towns. All symptomatic patients with positive serology for *T. canis* were referred for ophthalmological examination and were treated with albendazole in a dose of 10 mg kg^{-1} day^{-1} for 7 days. Patients weighing >40 kg received 400 mg albendazole a day for 7 days. All patients with bronchial asthma and CVA were treated with inhaled corticosteroid (ICS), as were patients whose histories revealed a beneficial effect of previously occasionally administered ICS. Further, short-term β_2-mimetics were sometimes administered as needed in cases of dyspnoea.

Blood samples were collected from each child to determine the larva-specific IgG antibodies and blood chemical parameters at the first presentation and after a

12-month follow-up period. At 2–3, 6 and 12 months their physical status, lung function, and demands for ICS and other medication were evaluated.

Informed consent to participation was obtained from parents and children aged 5 years and upward. All procedures are well documented in our patient record files. This study was approved by the Local Human Investigation Review Board of Albert Szent-Györgyi Medical and Pharmaceutical Center.

Statistical analysis

GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, California, USA) was used for statistical evaluation. Data are expressed as means ± standard error of the mean. Parametric data such as the blood eosinophil and absolute eosinophil counts, the total IgE level in the serum, the levels of specific IgG antibodies against *T. canis* antigen and the requirements for ICS at the beginning and end of the 12-month period, were calculated by using variance analysis and the paired or unpaired *t*-test. The chi-squared test was used to establish differences in BHR within the groups at the beginning and at the end of the study and in SPT results at the beginning of the study. $P < 0.05$ was considered significant. Non-parametric data, such as ages, were calculated by using the Mann–Whitney test between genders.

Results

Of the overall 425 children, 136 (32%) exhibited seropositivity for *T. canis* antigens, 43 (21 treated and 22 not treated against *T. canis*) of the 136 were unavailable for follow-up because they did not attend the control visits, but the remaining 93 were adequately assessed, diagnosed and followed up during 1 year. Table 1 shows the characteristics of these patients and the demand for ICS at the beginning of the study period. The seropositivity for *T. canis* was more prevalent among boys than among girls. The girls and boys did not differ significantly in terms of the peripheral eosinophil count, the absolute eosinophil count, *Toxocara* serology, the SPT findings as concerns either inhalative or nutritive allergens, non-specific bronchial provocations, the serum total IgE level or the demand for ICS. Since there was no significant gender difference, we decided to analyse the data on boys and girls together.

Table 1. Characteristics of patients with seropositivity for *Toxocara canis*. Values are given as means; IP, index of positivity; IP >12 was considered positive; ICS, inhaled corticosteroid. Percentages in brackets indicate prevalence of negative and positive results of skin prick tests and bronchial hyperresponsiveness among boys and girls.

	Boys	Girls
No. of patients	67	26***
Mean age (years)	7.1	8.7
Eosinophilic cells (%)	6.3	6.9
Absolute eosinophilic cells	468.9	498.3
Serum total IgE (IU ml^{-1})	544.6	692.1
Toxocara canis (IP)	37.3	32.1
Skin prick test		
No. of positive tests	43 (64%)	18 (69%)
No. of negative tests	24 (36%)	8 (31%)
Bronchial hyperreactivity		
No. of positive tests	27 (40%)	8 (31%)
No. of negative tests	29 (43%)	16 (61%)
No results obtained	11 (17%)	2 (8%)
Demand for ICS (μg day^{-1})	332	322

There was a significant difference in the numbers of boys and girls; ***$P < 0.001$.

Seroprevalence for Toxocara canis and chronic cough

The overall prevalence of *T. canis* seropositivity in the study population was 32%, as compared with 17% seropositivity in asymptomatic children ($P < 0.01$).

The diagnosis of bronchial asthma, NAEB or CVA was based on a history of attacks of dyspnoea and wheeze, the lung function, the BHR, the response to the bronchodilator and the susceptibility to atopy. Overall, 31 (33%) children were diagnosed with NAEB, 25 (27%) with CVA and 37 (40%) with bronchial asthma at the beginning of the study, as shown in table 2.

Eosinophil count, total IgE level and T. canis IgG level

The eosinophil count in the peripheral blood formed the basis of the patient classification. The 93 children were divided into two groups: 62 (group 1) with a decreased, and 31 (group 2) with an increased peripheral eosinophilic cell count at the end of the 12-month period. Table 3 shows their laboratory characteristics and the demand for ICS at the end of the study period. There were significant decreases in the levels of antibodies against *T. canis* and in the demand for ICS in both groups, and in the number of patients who received ICS in group 1. No significant difference was found in either group as concerns serum total IgE levels by the end of the 12-month period.

Efficacy of anthelminthics and ICS

Figure 1 shows the changes in the demand for ICS by the end of the 12-month period. At the beginning of the study, ICS was regularly administered to all patients with CVA and bronchial asthma and to five patients with NAEB whose histories revealed a beneficial effect of previously occasionally administered ICS. From the end of the second or third month of the study, ICS

Table 2. Distributions (number of patients (%)) of bronchial asthma, non-asthmatic eosinophilic bronchitis (NAEB) and cough variant asthma (CVA) at the beginning and at the end of the study.

	Before	One year later
NAEB	31 (33%)	31 (33%)
CVA	25 (27%)	17 (18%)
Bronchial asthma	37 (40%)	45 (49%)
Urban	3	8
Rural	34	37

Table 3. Laboratory characteristics of patients with seropositivity for *Toxocara canis* in group 1 (patients with a decreased eosinophil count) and group 2 (patients with an increased eosinophil count) before and at the end of the study. IP, index of positivity; IP >12 was considered positive; ICS, inhaled corticosteroid.

Characteristic	Group 1 (62 patients)		Group 2 (31 patients)	
	Before	One year later	Before	One year later
Eosinophilic cells (%)	8.1 ± 0.7	3.3 ± 0.4***	3.8 ± 0.6	6.1 ± 0.7***
Absolute eosinophilic cells	599.7 ± 55.0	270.5 ± 36.4***	256.1 ± 45.1	437.6 ± 51.3***
Serum total IgE (IU ml^{-1})	568.2 ± 99.7	423.4 ± 65.7	616.3 ± 147.5	603.4 ± 131.9
Toxocara canis (IP)	39.0 ± 6.5	18.5 ± 3.3**	30.4 ± 7.1	19.5 ± 4.5*
Number of patients receiving ICS	44	25***	23	20
Demand for ICS ($\mu g\ day^{-1}$)	317.7 ± 23.0	245.4 ± 23.9*	341.8 ± 31.3	232.1 ± 20.7***

Values are given as means ± SEM; significant differences between results before and at the end of the study in both groups are indicated as $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

administration was required in only two of those with NAEB and in 17 of the 25 with CVA.

At the first presentation, spirometry, bronchial reversibility tests and non-specific bronchus provocation tests could not be performed in 13 children aged <5 years because of a lack of cooperation. BHR was detected in 35 (44%) patients. By the end of the study period, the BHR was significantly improved in the cohort overall. A significant improvement in BHR was observed in those with CVA, in contrast with those with bronchial asthma in both groups (table 4).

Ophthalmological and chest X-ray examinations of seropositive children gave negative results.

Discussion

The purpose of the present study was to investigate the possible role of *Toxocara* infection and the prevalence of bronchial asthma, CVA and NAEB among patients with chronic cough. Laboratory parameters such as the eosinophilic cell count, the *Toxocara* serology and the serum total IgE level were assessed for their value in the setting-up of the diagnosis and at the end of the 1-year period. We examined the efficacy of early treatment with ICS and anthelminthics in children with CVA and bronchial asthma, and only with anthelminthics in those with NAEB.

Seroprevalence for Toxocara and chronic cough

In 93 patients with chronic cough who were observed during 1 year, bronchial asthma was diagnosed in 40%, CVA in 27% and NAEB in 33%. *Toxocara canis* seropositivity was more frequent in boys than girls. Great differences are observed worldwide in the overall prevalence of *Toxocara* infections. Sharghi *et al.* (2001) found that the overall prevalence of toxocariasis in children living in urban areas was 10.2%, whereas a

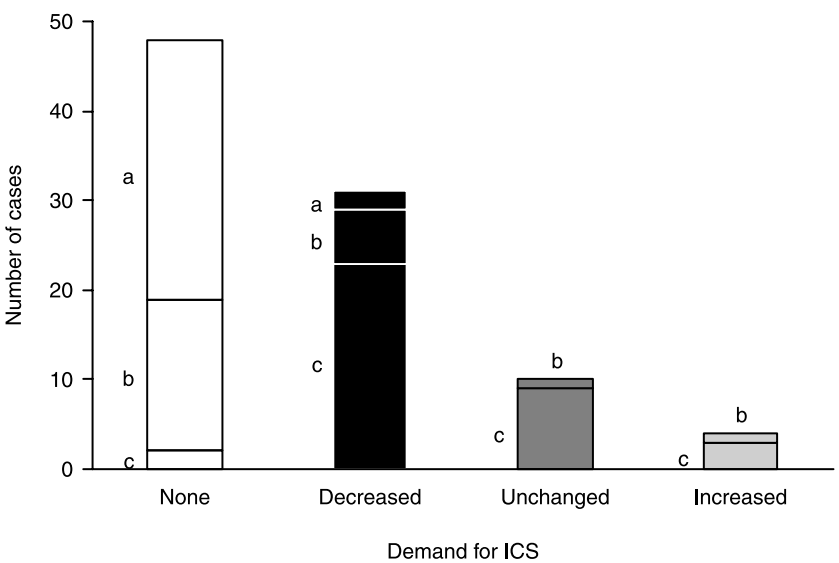

Fig. 1. Demand for inhaled corticosteroid (ICS) by patients with non-asthmatic eosinophilic bronchitis (a), cough variant asthma (b) and bronchial asthma (c) at the end of the 12-month period.

Table 4. Changes in bronchial hyperresponsiveness (BHR) during the 1-year period in patients with chronic cough ($N = 80$). NAEB, non-asthmatic eosinophilic bronchitis; CVA, cough variant asthma; BA, bronchial asthma; number of patients and distribution (%) of positive and negative results are indicated in each group (group 1: patients with a decreased eosinophil count; group 2: patients with an increased eosinophil count).

	Group 1 (53 patients)			Group 2 (27 patients)		
	NAEB ($N = 21$)	CVA ($N = 12$)	BA ($N = 20$)	NAEB ($N = 3$)	CVA ($N = 12$)	BA ($N = 12$)
Before						
BHR-positive	0	12 (100%)	9 (45%)	0	7 (58%)	7 (58%)
BHR-negative	21 (100%)	0	11 (55%)	3 (100%)	5 (42%)	5 (42%)
One year later						
BHR-positive	0	2 (17%)***	7 (35%)	0	1 (8%)**	10 (83%)
BHR-negative	21 (100%)	10 (83%)***	13 (65%)	3 (100%)	11 (92%)**	2 (17%)

Significant differences between results before and at the end of the study in both groups are indicated by $^{**}P < 0.01$; $^{***}P < 0.001$.

Brazilian study indicated a prevalence of 54.8% among children living in poor circumstances (Figueiredo *et al.*, 2005). The seroprevalence in developing countries may be 86% (Thompson *et al.*, 1986). A Hungarian national survey (unpublished data) indicated that the seroprevalence for *Toxocara* was significantly lower in healthy children than in those with chronic cough enrolled in the present study.

Some authors have reported a close association between seropositivity for *T. canis* and bronchial asthma (Buijs *et al.*, 1994; Oteifa *et al.*, 1998; Figueiredo *et al.*, 2005). The majority of our patients came from rural areas, which appeared to be an acceptable explanation for the 40% prevalence of bronchial asthma among seropositive children with chronic cough.

The published prevalence of NAEB varies between 10 and 30% (Brightling, 2006). Fujimara *et al.* (2003) concluded that NAEB is not a precursor of classic asthma. NAEB was diagnosed in 33% of our seropositive patients, and no members of this group became asthmatic.

Dicpinigaitis (2006) found that the one of the most important causes of cough is CVA. Lai *et al.* (2006) and Todokoro *et al.* (2003) reported CVA in 13.6% and 75%, respectively, of their cases with chronic cough. Although CVA seems to be more prevalent in Far Eastern countries, it is also an important entity in Europe, especially as regards the differential diagnosis of children with chronic cough (Bateman *et al.*, 2008). Recent data suggest that CVA is part of a continuum in the development of asthma symptoms and in the asthmatic inflammatory process (Abouzgheib *et al.*, 2007). Thirty to 54% of those with CVA develop typical asthma within several years (Todokoro *et al.*, 2003; Fujimara *et al.*, 2005). Nakajima *et al.* (2006) concluded that the majority of patients with CVA develop asthmatic symptoms after 1 year. We found that 8 of 25 patients with CVA (32%) presented asthmatic symptoms at the end of the 1-year period.

Eosinophil count, and total IgE and T. canis IgG levels

The basis of the patient classification was the eosinophil count in the peripheral blood. Sixty-two children (group 1) displayed a decreased, and 31 (group 2) an increased peripheral eosinophilic cell count. Some authors consider that there is a close positive association between toxocariasis and eosinophils and elevated IgE levels (Glickman *et al.*, 1987; Figueiredo *et al.*, 2005). The lower the eosinophilic cell count, the lower the *T. canis* IgG level and the lower the total IgE level observed in the serum in group 1. These three findings and symptoms are likely to be indicators of an improvement in the condition. The higher the eosinophilic cell count, the higher the total IgE level in those in group 2. These parameters and symptoms are likely to be predictors of a decline in the condition.

Efficacy of anthelminthics and ICS

A high helminth burden may alter the immune response and modify the prevalence of bronchial asthma. Exposure to mild or chronic *Toxocara* spp., leading to seropositivity, is associated with an increased prevalence of asthmatic symptoms, inducing a higher Th2 response with no activity of the regulatory system. In these cases, airway symptoms are alleviated after anthelminth treatment (Lynch *et al.*, 1987). The early administration of ICS is recommended for the effective treatment of CVA, with a view to restoration of the normal responsiveness of the bronchi and prevention of the progression of CVA to classic asthma (Shirahata *et al.*, 2005; Matsumoto *et al.*, 2006). Those patients who do not take ICS for a prolonged period develop typical asthma (Fujimara *et al.*, 2003, 2005). Presuming the aetiopathogenetic role of *T. canis* in the inflammatory process of chronic cough, we decided to treat the children not only with ICS, but also with a 1-week course of anthelminthics. Figure 1 shows that ICS therapy could be stopped after 2–3 months in 17 (68%) of the 25 with CVA. The other eight children might be candidates for bronchial asthma. Six of them needed only a decreased, and two an unchanged, or increased, dose of ICS at the end of the 1-year period. This may be explained by the fact that these children were exposed to contaminated soil in parks and playgrounds, either in urban areas or in rural communities, where infections had been acquired or re-acquired. These circumstances can cause a decline in the condition. Our experience and results support the observation that deworming therapy supplemented with ICS may prevent the transformation

of CVA into asthma in the majority of seropositive patients with chronic cough.

Toxocara canis may stimulate polyclonal IgE antibodies (Buijs *et al.*, 1994). IgE can bind to the membrane of bronchiolar and alveolar mast cells and release mediators that lead to inflammation of the bronchial mucosa and to asthma-like symptoms (Minvielle *et al.*, 1999), which can be alleviated by the use of effective anthelminthics. The patients with bronchial asthma required the long-term use of ICS; only two children were able to stop using it within 1 year. The dose of ICS was decreased significantly in 23 of the 37 (62%) children, while 12 (32%) needed an unchanged or an increased dose of ICS at the end of the 1-year period.

Brightling *et al.* (1999) regarded NAEB as a common cause of chronic cough. Since the aetiopathogenetic role of toxocariasis was assumed in the background of NAEB, only those patients who displayed no BHR and corresponded to the diagnostic criteria of NAEB participated in deworming treatment without ICS. *Toxocara canis* was the sensitizing agent identified in our cohort. It seemed that this therapy and optimal avoidance of sensitizers were sufficient; no-one needed ICS.

Toxocariasis in Hungary is mild or sporadic. Deworming therapy alleviates airway symptoms without exacerbation in patients with bronchial asthma and can be of definitive help for children with NAEB and the majority of those with CVA.

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