Rev. Inst. Med. trop. São Paulo
36 (1): 19-26, janeiro-fevereiro, 1994

CLINICAL AND LABORATORIAL FEATURES OF VISCERAL TOXOCARIASIS IN INFANCY (1)

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SUMMARY

Forty children with a diagnosis of Visceral Toxocariasis were evaluated prospectively from February 1982 to June 1989.

Diagnosis was established by clinical, laboratorial and serological (ELISA - ES *Toxocara canis* antigen) evaluations.

A great clinical polymorphism was found in our patients, ranging from unspecific or absent manifestations to an exhuberant symptomatology.

The laboratorial findings were: leukocytosis, eosinophilia and elevation of serum gammaglobulin and isohemagglutinin levels.

No significant relationship between clinical findings and laboratorial parameters was found. Serology (ELISA) was a method of great diagnostic support but did not show a correlation with clinical and laboratorial findings in this study. There was a significant relationship between pulmonary manifestations and the presence of signs and/or symptoms, when the patients were sent to us.

Our findings, especially the high incidence of pulmonary manifestations, suggest that Visceral Toxocariasis has to be included in the differential diagnostic of children with pulmonary manifestations, characteristic epidemiological data and associated eosinophilia.

KEYWORDS: Toxocariasis; Visceral larva migrans syndrome; infancy.

INTRODUCTION

Toxocara canis is the main agent of Visceral Larva Migrans Syndrome (VLMS) [6] which affects primarily 1-5-year old children [24,25]. They acquire the disease ingesting embryonate and viable eggs found in the soil. Contamination of public sites has been from 10-60%, according to reports in the literature [8, 10, 16, 17, 21].

Depending on the extent and intensity of impairment of the different systems, organs or tissues several clinical syndromes are defined at present. The classical form, characterized by pallor, prolonged fever, hepatosplenomegaly and alterations of the respiratory system is the mostly found [4, 7, 28] and the ocular form may be found either associated to the classical form or alone [26, 37].

More recently other relatively uncommon forms have been described. BASS et al., in 1983, described the so-called "Covert Toxocariasis" which manifests with

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abdominal pain, headache, cough and hepatomegaly. In these cases, the blood eosinophil percentages are not as high as in the classical form and can be normal despite the high serum *Toxocara* antibody titers [3].

In 1987, MAGNAVAL *et al.* described another clinical form affecting young female adults which manifests with chronic asthenia, pruritus and cutaneous rash, with pain at the right hypochondrium. Eosinophilia is moderated and the serum *Toxocara* antibody titers are very elevated [32].

Other clinical presentations described include among others: Guillain-Barré's syndrome [35], myocarditis [22] and subcutaneous nodules [18].

In general, in the visceral form there are leukocytosis with intense eosinophilia, hypergammaglobulinemia and isohemagglutinin titer elevation.

Diagnosis of Toxocariasis is based on clinical and laboratorial data due to difficulties in isolating the larva from tissues. ELISA serology using ES *T. canis* antigen is currently the method of choice for the diagnosis because it presents higher sensitivity and specificity than the formerly described techniques [12, 23].

There are few reports on human Toxocariasis among us, despite the favorable epidemiological conditions for its appearance, as emphasized by RODRIGUES DA SILVA in 1957 [36] and PESSOA in 1973 [34].

The first Brazilian report on Visceral Toxocariasis (VT) was described by FERRAZ et al. in 1980 [20]. Thereafter, other studies [1, 9, 11, 19, 29, 30, 31] have contributed to the understanding of this pathological entity.

The objective of the present study is to report clinical and laboratorial characteristics of the different forms of VT presentation in infancy, emphasizing its presence among us and the need for a better knowledge of this clinical entity.

CASES AND METHODS

From February 1982 to June 1989 we evaluated prospectively 40 children (ratio male/female = 1.35; age ranging from 1 year and 4 months to 8 years and 7 months, mean of 2 years and 9 months) who were sent to our Hospital and whose diagnosis of VT was established based on the existence of two mandatory criteria associated to at least one of the secondary criteria described below.

Mandatory criteria:

1. Number of eosinophils $\geq$ 2000/mm3.
2. Serum *Toxocara* antibody titer (ELISA method) $\geq$ 1/640.

Secondary criteria:

1. Anemia, hepatomegaly and/or pulmonary symptoms.
2. Geophagia, onicophagia and/or household contact with dogs during the last two years.
3. Hypergammaglobulinemia, isohemagglutinin titer $\geq$ 512 (anti-A and/or anti-B) or serum immunoglobulin levels exceeding two standard deviations of the mean for age [33].

The patients were divided into two groups according to reason for which they were sent:

Group A (14 cases): asymptomatic, sent in order to elucidate the cause of eosinophilia found at routine blood count.

Group B (26 cases): symptomatic, as shown in Table 1.

All children were underwent a complete history and physical examination, including ophthalmological evaluation and the following tests: blood count, plasma protein electrophoresis, immunoglobulin and transaminase determinations, isohemagglutinin titers, rheumatoid factor investigation, feces parasitology, *Toxocara* serology and chest X-ray.

Toxocara serology was performed by the immunoenzymatic method according to DE SAVIGNY & VOLLER [13, 14] modified by BACH-RIZZATTI [2]. The plates were sensitized with Antigen ES (excretion and secretion antigen of larval *Toxocara canis*). All samples of sera were absorved previously with *Ascaris suum* antigen. Samples of standard reacting and nonreacting serum were included in all plates as controls.

Mann-Whitney's test for two independent samples was used for the statistical analysis of laboratory data for groups A and B and Fisher's exact test for that of the association between pulmonary manifestations and groups A and B [38].

RESULTS

The epidemiological findings found in our cases were geophagia in 80% of the cases and household contact with dogs during the last two years, in 66.7% of the cases.

Regarding the reasons for which the cases were sent (Table 1), [13] patients presented pulmonary manifestations, being 50% of group B.

Table 1

Reason for sending of 26 symptomatic patients with toxocariasis (Group B).

Reason	Nº of Cases	%
Pulmonary manifestations	13	50.0
Fever	4	15.4
Joint manifestations	2	7.7
Adenomegaly	1	3.8
Generalized edema	1	3.8
Decrease in muscular strength in LLEE*	1	3.8
Diarrhea	1	3.8
Increase in abdominal volume	1	3.8
Asthenia and pain in LLEE*	1	3.8

* LLEE - Lower Extremities

The presentation forms observed in Visceral Toxocariasis in these cases had a great variability of manifestations: asymptomatic, classical and atypical forms.

The asymptomatic group (n = 14) when submitted to the several steps of clinical evaluation showed only one patient with a normal physical examination.

Thirty-eight patients, including the atypical forms, presented some clinical findings compatible with the classical form of VLMS including: skin pallor (70%), abnormal lung auscultation (60%), hepatomegaly (50%) and splenomegaly (20%).

Atypical forms included: Guillain-Barré's syndrome, arthritis mimicking juvenile rheumatoid arthritis, generalized edema and severe respiratory failure with a diffuse interstitial pattern on chest X-ray.

All patients were submitted to ophthalmological evaluation without detecting ocular impairment due to Toxocariasis.

Regarding laboratorial data, hemoglobin level varied from 5.0 g/dl to 14.5 g/dl, with 26 cases (65%) presenting hemoglobin lower than 11 g/dl and 18 cases with levels below 9.5 g/dl.

The total leukocyte number, the number of eosinophils (absolute and percentage), gammaglobulin values, serological and isohemagglutinin titers are shown in Figures 1-6.

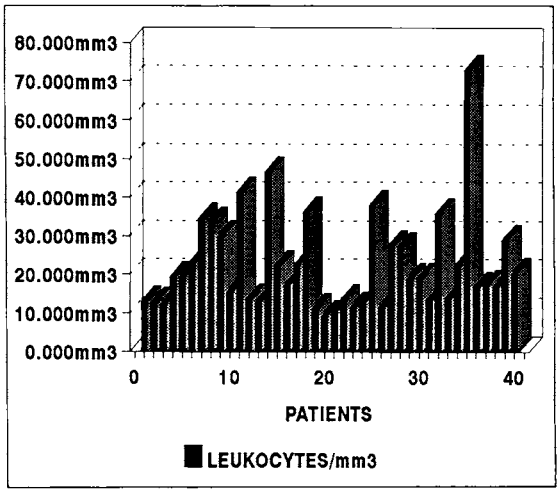

Fig. 1 - Absolute leukocyte number in 40 toxocariasis patients.

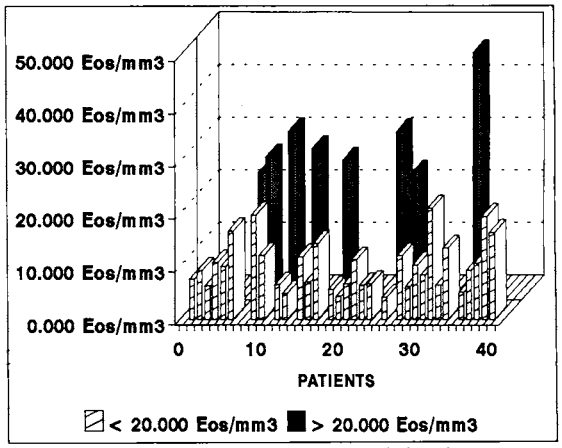

Fig. 2 - Absolute eosinophil number in 40 toxocariasis patients.

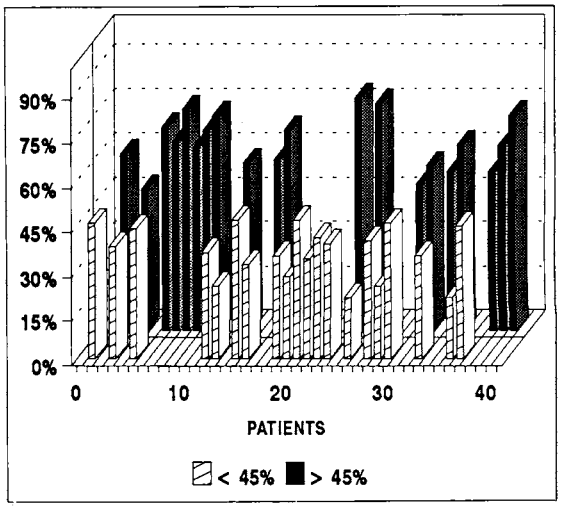

Fig. 3 - Eosinophil percentage in 40 toxocariasis patients.

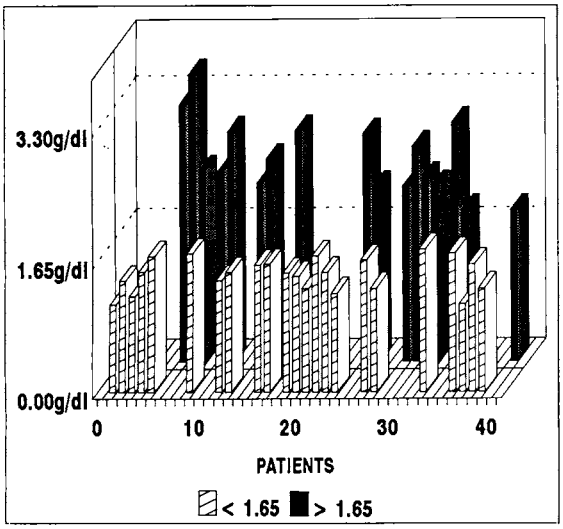

Fig. 4 - Serum gammaglobulin levels in 40 toxocariasis patients.

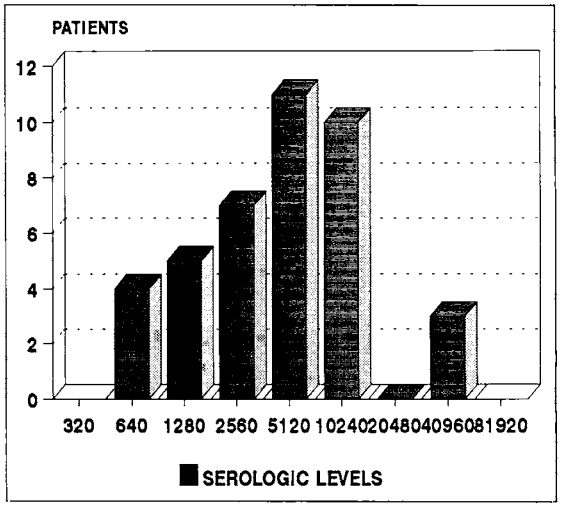

Fig. 6 - Distribuition of serologic toxocara levels (ELISA) in 40 toxocariasis patients.

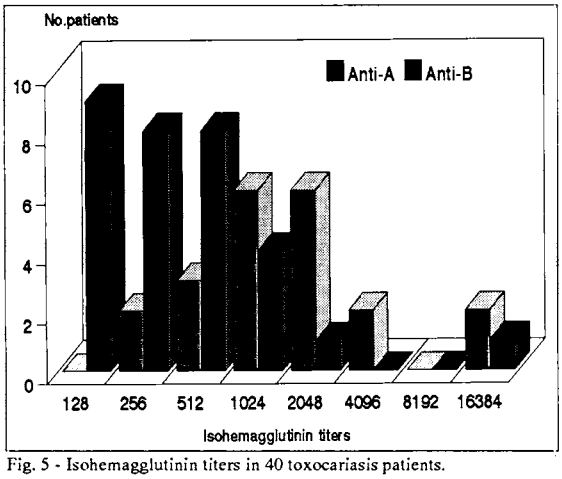

Fig. 5 - Isohemagglutinin titers in 40 toxocariasis patients.

Feces parasitology was positive in 29 samples (72.5%), the mostly found agents being *Trichuris trichiura* in 52.5% and *Ascaris lumbricoides* in 25% of the cases.

Radiologic chest evaluation for lung fields showed alterations in 30% of the cases, 4 showing bronchopneumonia, 6 reinforcement of the vasobronchial network, 3 interstitial process and 1 atelectasis.

Statistical analysis of laboratory data did not show significant differences between Groups A and B (Table 2).

Leukocyte variables regarding these groups, although not showing statistically significant differences, present values of z close to the critical value.

Table 2

Laboratorial data of group A and B patients with toxocariasis

Group	Leucocytes /mm3	Eosinophils %	Eosinophils /mm3	Gammaglobulin g/dl	Serology* (ELISA)
A	17,657 (SD 7,835.7)	45.1 (SD 17.3)	8,808 (SD 6.812)	1.61 (SD 0,52)	7,697 (SD 10,141) 4.9701* (SD 5.2967)
B	24,938 (SD 14,098)	47.8 (SD 16,1)	13,213 (SD 10.328)	1.82 (SD 0,69)	7,673 (SD 10,257) 4.1509* (SD 4.7539)
z	1.9565	0.5387	1.3610	0.8223	0.0992
1-p	0.9488	0.3577	0.8262	0.5878	0.0718

MANN-WHITNEY's test for z crit = 1.96 ($p \leq 0.05$)

* Mean geometrical titer

The presence of pulmonary manifestations detected on physical examination was analyzed statistically in relation to Groups A and B; a significant correlation could be noted regarding pulmonary impairment in Group B patients (Table 3).

Table 3

Pulmonary alterations vs reason for sending in 40 toxocariasis patients

Pulmonary alterations	Group A	Group B	Total
Present	5	19*	24
Absent	9	7	16
Total	14	26	40

FISHER's test p = 0.02502*

* Statistically significant

DISCUSSION

Since the first report by BEAVER [4] on the classical clinical manifestations of human Toxocariasis, other forms of presentation have been described, rendering the understanding of the natural history of this disease still more complex [31, 41].

Among us, despite the favorable conditions for its appearance, human Toxocariasis is still a little diagnosed pathology.

The epidemiological data found in our cases should be analyzed considering that many children stayed in day nurseries, rendering information subject to errors. In addition, *Toxocara canis* eggs are extremely resistant to hostile factors and may remain viable in the soil for a long time [40]. Therefore, even if there is no recent household contact with dogs, the possible ingestion of viable embryonate eggs can not be ruled out.

Concerning clinical features, it should be emphasized that those patients without complaints, presenting only eosinophilia, may belong to different evolutionary phases of the disease. In those cases there is the possibility that eosinophilia persists for a longer time than the characteristic clinical manifestations of the symptomatic phase of the disease.

In addition, 25% of our cases presented ascaridiasis with more than two different parasites being detected in 27.5%; therefore the eosinophilia in these patients may also be due to this fact and not exclusively to infection from *Toxocara*.

Pulmonary manifestations were frequent and variable, according to former reports [15, 18, 28] and one of our patients presented severe respiratory failure with a radiological picture of interstitial pneumonia. This manifestation may represent a host hypersensitivity reaction to the presence of the larva or to the release of antigens or substances produced by the parasite [7]. This same pathophysiological mechanism may be involved in joint manifestations and in the edematous form found in our patients, since other causes were excluded.

The presence of immune complexes during the acute phase of the disease may be another pathophysiological mechanism associated to joint manifestations.

The neurological manifestations found in our cases have been described by several authors [18, 28, 35] and include: Guillain-Barré's syndrome, seizures and behavioral disorders.

Several mechanisms may be involved in this group of patients, such as the presence of immune complexes and the larva itself in brain tissue, as has been described by HILL [27].

Other clinical manifestations found in our cases included pallor and hepatomegaly. It should be noted that these findings could be due to other causes and not necessarily to Toxocariasis since many children presented a history of iron deficient feeding and treated verminosis.

With regard to fever, only 6 of our patients presented this clinical data (15%) while other authors report a frequency of 35 to 80% [18, 28, 39].

This difference between our findings and the literature may be attributed to the fact that most of the described cases were only patients with clinical symptoms while our cases comprised 35% of asymptomatic patients with eosinophilia.

Analyzing the physical examination data of group A patients we noted that although they did not present complaints, there were important manifestations when they were submitted to a more detailed clinical evaluation.

This group can present peculiar clinical characteristics due to the parasite load, to particularities of the immune response or even to the duration of the infection. Regarding laboratorial data it should be noted that

in our cases, the absolute number of eosinophils of more than or equal to 2000/mm^3 was used as inclusion criteria, while some authors use the percentage of eosinophils - 20 to 30%. If we adopted as criteria the percentage of 20%, the diagnosis would not have been made in 2 patients and in 6 cases if it were 30% (fig. 4). Thus, it seems that the absolute eosinophil not the percentage is a more sensitive criteria to detect Toxocariasis cases.

Even with the recent descriptions by TAYLOR [41, 42] and MAGNAVAL [32] of the possibility that Toxocariasis eventually is not associated to eosinophilia, a further reevaluation of our criteria may be worthwhile. Hypergammaglobulinemia was found in 92.5% of the cases, while HUNTLEY [28] reports it in 60% of the patients. It is thought that it is a consequence of a polyclonal activation due to the chronic release of different antigens of the parasite.

Elevation of isohemagglutinin titers was quite significant; it was suggested that this elevation occurs because of the similarity between antigens of the parasites and those of human erythrocytes.

The radiologic study of the chest showed alterations in 30% of the patients, with different radiologic patterns. GLICKMAN [24] found 50% transient alterations on radiology, while HUNTLEY [28] described a higher frequency of peripheral infiltrates.

Toxocara serology by the ELISA method is an important laboratorial data in the diagnosis of VT, although the significance of the titers still remains unclear with high titers being found in 2.6% of asymptomatic adults [15].

Only those patients who presented serological titers higher than or equal to 640 were selected for our evaluation. These titers were referred by BACH-RIZZATTI [2] as those found in patients with clinical manifestations suggestive of the acute phase of VT and which remained even after absorption with *Ascaris suum* antigens.

In our cases the titers varied from 640 to 40960 with 60% of the patients presenting titers higher than or equal to 5120. In this study serology did not allow to differentiate patients in the acute phase of the disease and did not correlate with the clinical and/or laboratorial variables.

Interestingly most patients with clinical symptomatology presented mainly pulmonary manifestations. Since the number of cases could be a limiting factor for further conclusions, other studies with a greater number of patients should be conducted. Our data indicate that Visceral Toxocariasis is a disease with a great variability of clinical expressions from exuberant manifestations to totally asymptomatic pictures, where eosinophilia may be the only finding to suggest this diagnosis. The authors propose the inclusion of this clinical entity in the differential diagnosis of eosinophilic syndrome of infancy in our country. It is also suggested that this disease may be an important cause of pulmonary manifestations and it should be considered in chidren with suggestive epidemiology.

The finding of similar serological and laboratorial values with contrasting clinical manifestations suggests that we may be analyzing different periods of the disease whose comparison may not be possible.

RESUMO

Aspectos clínicos e laboratoriais da toxocaríase visceral na infância

Quarenta crianças portadoras de Toxocaríase Visceral foram avaliadas, prospectivamente, de fevereiro de 1982 a junho de 1989.

O diagnóstico foi estabelecido através de avaliações clínicas, laboratoriais e sorológicas (ELISA - Antígeno ES de *Toxocara canis*).

Em nossos pacientes encontramos grande polimorfismo clínico, desde quadros inespecíficos ou assintomáticos até sintomatologia exuberante, sendo as manifestações pulmonares as mais frequentes.

Os achados laboratoriais foram: leucocitose, eosinofilia, elevação dos níveis de gamaglobulina e dos títulos de isohemaglutininas séricas.

Não encontramos relação significante entre os achados clínicos e os parâmetros laboratoriais, incluindo a sorologia, apesar desta ser um teste de grande auxílio diagnóstico.

Nossos achados, especialmente a alta incidência de manifestações pulmonares, sugerem que a Toxocaríase Visceral deve ser incluida no diagnóstico diferencial de crianças que apresentam manifestações pulmonares, dados epidemiológicos característicos e eosinofilia associada.

ACKNOWLEDGEMENT

The authors are indebted to Drs. Pedro Paulo Chieffi and Maria Helena Kiss for valuable suggestions, to Dr. Marcelo Brandão for his contribution and to CAPES for the fellowship granted.

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Recebido para publicação em 21/06/1993.
Aceito para publicação em 28/10/1993.