

PARASITIC CAUSES OF HEPATOMEGALY IN CHILDREN

By

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ABSTRACT

Three hundred children with hepatomegaly were selected. They were subjected to full clinical and laboratory examinations. Also serum samples were examined to detect IgG using ELISA against SEA, chromatography purified hydatid cyst antigen, commercially available *Toxoplasma* antigen, partially purified adult *Fasciola* antigen and second-stage larvae *Toxocara canis* antigen. IHAT was used to detect IgG against *Toxoplasma* and *T. canis*. A commercially available IHAT kit for leishmaniasis was used. Based on immunological assays, 125 cases were suffering from various parasitic infections. Thirty cases with schistosomiasis (10%), 26 cases fascioliasis (8.7%), 18 toxocariasis (6%), 35 toxoplasmosis (11.7%), 3 cases hydatidosis (1%) and 13 cases mixed parasitic infections. No parasitic causes could be found in 175 cases (58.3%). Moderate or marked hepatomegaly favours the presence of schistosomiasis. Whereas, most cases with other parasites and those with non-parasitic infections fall in the category of mild hepatic enlargement. There was no associated splenomegaly in cases with *Fasciola*, *Toxocara*, hydatid disease and/or the non-parasitic group. Most of hepatomegalic cases with non-parasitic causes were found to be associated with fever (88.5%). Fever was found in nearly 50% of cases with either *Toxoplasma* or *Toxocara* infections. Mild eosinophilia was found in all cases with parasitic causes. Only 24 cases of non-parasitic group (13.7%) had eosinophilia. Moderate and high eosinophilia were found in cases with fascioliasis and toxocariasis. Cases with fascioliasis had a statistically

significant increase in enzymes activities specially alkaline phosphatase. It was concluded that parasitic infections should be considered as an important cause of liver enlargement in children. Serological methods using purified antigenic fractions are an important tool for diagnosis.

INTRODUCTION

Many parasitic diseases can cause hepatomegaly. One of the most important parasitic causes is the infection with larval stage of the cestode species *Echinococcus granulosus* causing hydatidosis. It is an important zoonotic endemic parasitic disease of many temperate and equatorial regions of the world (Fouad, 1986). The liver is the organ most often involved, followed by the lungs, then mesentery, spleen and pancreas (Menghelli et al., 1992). Clinical diagnosis of hydatidosis could be misleading as signs and symptoms are often non-specific and disease induces a picture of space occupying lesion in the affected organ (Kaddah et al., 1992). Diagnosis is based on imaging techniques coupled with immunodiagnostic procedures. Using different immunological techniques, kaddah et al. (1992) reported that ELISA was a good screening test as it gave 88% sensitivity and 89% specificity. Schistosomiasis has been described as an immunological disease in which major manifestations are due to inflammatory reactions around parasite eggs entrapped in the liver or urogenital system (Warren, 1975). The liver is the main organ that is affected by *S. mansoni* infection due to granulomatous reactions that lead to hepatomegaly, portal hypertension and splenomegaly (El-Hawey et al., 1985). Disabling morbidity in *S. mansoni* infections are generally not caused by intestinal lesions but arise from portal hypertension due to the hepatosplenic form of the disease (Gryseels, 1992). In the disease, recovery of eggs is difficult. Other parasitological techniques, such as rectal or hepatic biopsy are not always possible, time consuming and uneconomic as they must be repeated. So, dependence on immunological methods in diagnosis has increased in recent years (Khalil et al., 1994). Liver involvement has been reported in both acute and chronic forms of toxoplasmosis (Weitberg et al., 1979). The disease is a common protozoal disease of a world-wide distribution. The diagnosis of the disease depends on serological data, since clinical manifestations resemble many other diseases and isolation of the parasite from patients is usually difficult. Even in congenital toxoplasmosis, liver affection may occur as Mayer et al. (1989), diagnosed a case of congenital toxoplasmosis in a foetus born to a diseased

woman by ultrasound scan and they found a sever hydrocephalus with hepatomegaly and ascites. Warren and Mahmoud (1990) stated that the entity of *Toxoplasma* hepatitis is controversial and has not been proven to exist, although hepatomegaly is not uncommon in acquired toxoplasmosis and abnormal liver function tests may present. Toxocariasis is more common in children and characterized by the formation of granulomatous reactions in various tissues (Garavelli, 1988). The clinical features of toxocariasis include eosinophilia associated with hepatic enlargement, fulmenary infiltration, gastrointestinal symptoms, central nervous system disturbances and myocarditis (Zinkham, 1978). Taylor et al. (1988) reported that the clinical features are generally non-specific and toxocariasis should be considered in any case suffering from recurrent abdominal pain and liver enlargement. Diagnosis depends on biopsy and serological tests to detect antibodies and antigens. Khalil et al. (1989) found that IFAT and ELISA were the most reliable tests regarding sensitivity and specificity. They also found that egg antigen was more sensitive than adult worm antigen. Fascioliasis has a cosmopolitan distribution and is prevalent in sheep raising countries. It is an increasingly important parasite of man in many Mediterranean countries including Egypt (Farag et al., 1979). The most important clinical manifestations are fever, weight loss, hepatomegaly, right hypochondrium pain and diarrhoea with high eosinophilic count usually exceeding 25% (Alvarez et al., 1992). Diagnosis is based on the recovery of eggs in stool samples usually on using concentration techniques (Knoblock et al., 1985). However, eggs do not appear during the prepatent period, so different immunological techniques may be useful in the diagnosis (Santiago et al., 1984).

Leishmania infantum is the main *Leishmania* species responsible for visceral leishmaniasis in the Mediterranean Countries (WHO, 1990). Egypt was actually considered to be visceral leishmaniasis free country (Rifaat et al., 1968). However, Faris et al. (1986) detected 20 cases of visceral leishmaniasis in the vicinity of Al-Agamy, Alexandria. Moreover, Khalid et al. (1982) and Morsy et al. (1983, 1985) found a serological evidence for host incrimination of dogs in Cairo, Alexandria and Assuit Governorates respectively. Nodoubt, infantile VL is known in Egypt (Morsy, 1988). The disease ranges from asymptomatic through subclinical to overt disease manifested mainly by fever and hepatomegaly (Badaro et al., 1989). The sure method of diagnosis is the demonstration of the parasite in spleen, bone marrow or lymph glands. Spleen puncture, however, requires strict

precautions and should only be practiced by experienced medical staff. Serological examination is the easiest and the most efficient screening procedure particularly for large-scale epidemiological studies.

The aim of the present work is to study the role of the parasitic infections among children with hepatomegaly.

SUBJECTS AND METHODS

Four thousands school children from three different villages in Sharkia Governorate and the outpatient clinics of El-Menia University hospital were examined to select 300 cases with hepatomegaly. Complete history for these cases was investigated with emphasizing about previous attacks of hemolytic anemia, recurrent fever with unknown origin, play habits with dogs or cats, swimming habits or contact with water, and mother troubles of miscarriage or family history of toxoplasmosis. All cases were subjected to full clinical examination with special concern to liver and spleen enlargement, the firmness of the liver, nodules and its edge. Stool examination, using modified kato thick smear method (Martin and Beaver, 1968), was performed to detect infection with parasites. Urine was examined using nuclepore filtration technique (Peters et al., 1976). Complete blood picture with eosinophilic count was performed for all cases, and any case with hemolytic anemia or leukaemia was excluded from the study. Liver function tests including SGOT & SGPT levels and alkaline phosphatase activities were determined. Serum samples for the 300 cases were examined to detect IgG using ELISA against: soluble *S. mansoni* egg antigen (Hassan, 1987) for schistosomiasis; chromatography purified hydatid cyst antigen for hydatidosis; commercially available antigen for toxoplasmosis, partially purified adult *Fasciola* antigen (Hassan et al., 1995) for fascioliasis and second-stage larvae *T. canis* antigen (Cypess et al., 1977) for toxocariasis. IFAT was used to detect IgG against: commercially available *Toxoplasma* antigen for toxoplasmosis and second-stage larvae *T. canis*. Moreover, a commercially available IHAT kit for diagnosis of leishmaniasis was used.

RESULTS AND DISCUSSION

Among 4000 school children from 3 different village in Sharkia Governorate and the outpatient clinics of El-Menia University hospital, 300 cases with hepatomegaly and without any paediatric or hemolytic causes

were investigated serologically. 125 (41.6%) cases were suffering from various parasitic infections as they had a high antibody titer, above the cut-off values of normal controls, on using different serological methods. The parasitic cases were distributed as follows: 30 cases pure schistosomiasis (10%), 26 cases fascioliasis (8.7%), 18 toxocariasis (6%), 35 toxoplasmosis (11.7%), 3 cases hydatidosis (1%) and 13 cases mixed parasitic infections. The mixed infections included 6 cases infected with both *Schistosoma* and *Toxoplasma*, 3 with *Schistosoma* and *Fasciola*, 3 with *Toxoplasma* and 1 case with *Fasciola* and *Toxoplasma*. No parasitic causes could be found in 175 cases (58.3%) as shown in Table (1).

Out of 39 serologically proven cases of schistosomiasis, 20 had *S. mansoni* viable eggs in their faeces, 2 with *S. haematobium* ova in urine and 1 case showed a mixed infection. Moreover, 21 out of 30 serologically positive fasciolosis cases were found to have *Fasciola* eggs in their stools.

Table (2) showed the degree of liver enlargement. There was a statistically significant difference ($P < 0.01$) only between cases with schistosomiasis and those with non-parasitic infections, showing that moderate or marked hepatomegaly favours the presence of

schistosomiasis. On the other hand, most cases with other parasites and those with non-parasitic infections fall in the category of mild hepatic enlargement. In experimentally infected mice, Eissa et al. (1990) reported that liver affection was mild to moderate in chronic toxoplasmosis infection.

In this study, there was no associated splenomegaly with hepatomegaly in cases with *Fasciola*, *Toxocara*, hydatid disease and/or the non-parasitic group. On the other hand, *Schistosoma* and *Toxoplasma* infections showed a statistically significant difference ($P < 0.001$ and < 0.05 respectively) when compared with the non-parasitic group as shown in Table (3). The portal hypertension occurred in schistosomiasis as a result of the periportal fibrosis leads to splenic congestion and enlargement. In toxoplasmosis, liver affection occurs with generalized infection that is usually associated with other organ involvement including spleen (Frenkel and Remington, 1980). Most of hepatomegaly cases with non-parasitic causes were found to be associated with fever (88.5%). Table (4) showed that fever was found in nearly 50% of cases with either *Toxoplasma* or *Toxocara* infections. The statistical analysis of the results revealed that fever is not a characteristic feature of parasitic infections.

In this work, eosinophilia ($> 10\%$) was found in all cases with hepatomegaly of parasitic causes. On the other hand, only 24 cases of

non-parasitic group (13.7%) had eosinophilia. Moderate (10-20%) and high (> 20%) eosinophilia were associated with fascioliasis and toxocariasis. The results showed a highly significant difference ($P < 0.001$) in these 2 groups when compared with the non-parasitic group (Table 5). Alveraz et al. (1992) reported that the high eosinophilic count usually exceeding 25% is a characteristic feature of fascioliasis. Toxocariasis was also found to be associated with high eosinophilia (Zinkham, 1978).

Table (6) showed the results of liver function tests in various parasitic and non-parasitic groups in comparison with a control group (without hepatomegaly). A statistically significant difference in the activity of the 3 enzymes between non-parasitic group of hepatomegaly and control group was found, denoting that liver enlargement due to causes other than parasitic

Table (1) : Percentage of parasitic causes of hepatomegaly.

Causative agents		No. of cases	Percentage
Parasitic causes	Toxoplasmosis	35	11.7%
	Schistosomiasis	30	10%
	Fascioliasis	26	8.7%
	Toxocariasis	18	6%
	Hydatidosis	3	1%
	Mixed infections	13	4.3%
	Visceral leishmaniasis	0	0%
Non-parasitic causes		175	58.3%

Table (2) : Relation between liver enlargement and parasitic infections.

Liver Infection	Mild		Moderate		Sever		P value
	No.	%	No.	%	No.	%	
<i>Schistosoma</i>	21	54	17	43.5	1	2.5	< 0.01
<i>Fasciola</i>	25	83	4	14	1	3	> 0.05
<i>Toxoplasma</i>	41	91	4	9	0	0	> 0.05
<i>Toxocara</i>	19	90.5	2	9.5	0	0	> 0.05
Hydaud	3	100	0	0	0	0	> 0.05
non-parasitic	175	100	0	0	0	0	

Table (3) : Relation between presence of spleen enlargement and parasitic infections.

Spleen Infection	Enlarged		non-enlarged		P value
	No.	%	No.	%	
<i>Schistosoma</i>	15	38.5	24	61.5	< 0.001
<i>Fasciola</i>	0	0	30	100	> 0.05
<i>Toxoplasma</i>	13	29	32	71	< 0.05
<i>Toxocara</i>	0	0	21	100	> 0.05
Hydatid	0	0	3	100	> 0.05
non-parasitic	0	0	175	100	

Table (4) : Relation between presence of fever and parasitic infections.

Fever Infection	Present		Absent		P value
	No.	%	No.	%	
<i>Schistosoma</i>	5	13	34	87	< 0.001
<i>Fasciola</i>	2	7	28	93	< 0.001
<i>Toxoplasma</i>	21	47	24	53	< 0.01
<i>Toxocara</i>	10	48	11	52	< 0.01
Hydatid	0	0	3	100	< 0.001
non-parasitic	155	88.5	20	11.5	

Table (5) : Relation between parasitic infections and eosinophilia.

Eosinophilia Infection	Mild		Moderate		Sever		P value
	No.	%	No.	%	No.	%	
<i>Schistosoma</i>	21	54	14	36	4	10	> 0.05
<i>Fasciola</i>	2	7	6	20	22	73	< 0.001
<i>Toxoplasma</i>	14	31	19	42	12	27	< 0.01
<i>Toxocara</i>	2	10	4	19	15	71	< 0.001
Hydatid	0	0	2	67	1	33	> 0.05
non-parasitic	16	67	8	33	0	0	

Table (6) : Liver function tests among patients with parasitic infections.

Tests Infection	SGOT		SGOT		ALK. PHOSPHI	
	Mean \pm S.D.	P Value	Mean \pm S.D.	P Value	Mean \pm S.D.	P Value
Control	20 \pm 5.5		18 \pm 4.1		12 \pm 3.7	
non-parasitic	26 \pm 11.2	< 0.05	24 \pm 12.1	< 0.05	17 \pm 7.5	< 0.05
<i>Schistosoma</i>	22 \pm 4.5	P ¹ > 0.05 P ² < 0.05	21 \pm 4	P ¹ > 0.05 P ² > 0.05	12 \pm 4.4	P ¹ > 0.05 P ² < 0.01
<i>Fasciola</i>	32 \pm 14.6	P ¹ < 0.01 P ² > 0.05	31 \pm 15.2	P ¹ < 0.01 P ² < 0.05	23 \pm 4.2	P ¹ < 0.01 P ² < 0.01
<i>Toxoplasma</i>	23 \pm 8.2	P ¹ > 0.05 P ² > 0.05	21 \pm 7.5	P ¹ > 0.05 P ² > 0.05	15 \pm 7.4	P ¹ > 0.05 P ² > 0.05
<i>Toxocara</i>	22 \pm 1	P ¹ > 0.05 P ² < 0.05	20 \pm 0.4	P ¹ > 0.05 P ² < 0.05	11 \pm 6.3	P ¹ > 0.05 P ² < 0.05
Hydatid	23.5 \pm 1.5	P ¹ > 0.05 P ² > 0.05	19.5 \pm 1.5	P ¹ > 0.05 P ² > 0.05	16.5 \pm 2.5	P ¹ > 0.05 P ² > 0.05

infections is usually associated with certain degree of liver functions. Cases with fascioliasis had a statistically significant increase in enzymes activities when compared with the control group specially in alkaline phosphatase activity. No significant difference between the other parasitic causes and the control group was detected. This result is more or less in agreement with those of Barret-Conner (1986) who found that alkaline phosphatase was raised in all cases of fascioliasis while transaminases were raised in most cases.

IHAT was used in this study to detect visceral leishmaniasis. However, no cases were found. This agreed with the known idea that Egypt was free from this disease (Rifaat et al., 1968). The 22 cases that were detected near Alexandria by Tawfik et al. (1983) and Faris et al. (1986), could be considered as sporadic I.VL. cases as they were found in young children. Morsy et al. (1992) in a study in Sharkia Governorate, reported a 30 years old man with lymphatic leishmaniasis but without visceral involvement. Also, Morsy et al. (1990) found that IHAT was simple and sensitive test for VL. but less specific as it crossly reacted with filariasis, strongyloidiasis, hymenolepiasis and ascariasis. These authors reported that the diagnostic titre should be raised at least to 256 in order to increase the specificity of the test.

The prevalence of different parasitic infections in this work, is generally agreed with these of previous results. Hydatidosis is an important zoonotic disease of many Mediterranean countries, whereas the prevalence is not high in humans (Fouad, 1986). Toxoplasmosis affects about 30% of the human races, varying in different localities from 5% to 90% (Manson-Bahr and Bell, 1987). In this work, the prevalence was slightly lower (15%) as hepatomegaly is not the characteristic feature of the disease. Taylor et al. (1988) reported an overall prevalence of 6% and 8%, of those under 15 years of age, with toxocariasis by the detection of serum antibodies. This agreed with present results (7%), however, Abdel Fattah et al. (1992) found a prevalence of 4% positive *Toxocara* antibodies in Zagazig. This difference may be due to the different antigen used in the ELISA assay.

Moreover, fascioliasis is now considered as an important parasitic infection in Egypt. In Sharkia Governorate, Makled et al. (1988), reported 9% prevalence and Hassan et al. (1995) found it as high as 10.9% among school children. Abou-Basha et al. (1990), found that human fascioliasis is becoming a parasitological problem of increasing threat in the vicinity of Alexandria. Also, in Dakahlia Governorate human fascioliasis became a

parasitic health problem (El-Shazly et al., 1991).

It was generally concluded that parasitic infections should be considered as an important cause of liver enlargement in Children. Serological methods using purified antigenic fractions are an important tool for diagnosing parasitic diseases beside the stool examination techniques specially for schistosomiasis and fascioliasis. The following points should be taken into consideration: First, eosinophilia is usually present in parasitic infections specially fascioliasis and toxocariasis which are associated with characteristically high eosinophilic count. Second, the liver enlargement is usually mild or moderate in parasitic diseases except schistosomiasis in which hepatomegaly is moderate or severe and usually associated with splenomegaly. Third, fever is not a characteristic feature associated with parasitic infections. Finally, liver function tests are usually not altered in parasitic infections except with fascioliasis in which the level of alkaline phosphatase is significantly elevated.

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