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INFLUENCE OF THE HOST RELATED FACTORS IN THE DEVELOPMENT OF THE HEPATOSPLENIC FORM OF SCHISTOSOMIASIS MANSONI

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The frequency of hepatosplenomegaly in endemic areas is not proportional to the fecal ova count. This may be explained by epidemiological genetic. The occurrence of two or more cases of schistosomal hepatosplenomegaly in nuclear family is much higher than expected. The concentration is higher among siblings than it is among mothers and children of father and children. It is not significant between father and mother.

If the mother, instead of the father, has hepatosplenic schistosomiasis the relative risk for the child to acquire hepatosplenomegaly is at least five times (the maternal affect). The inbreeding is higler in the hepatosplenic than in the hepatointestinal patients.

In some areas in Brazil the hepatosplenic form of the schistosomiasis mansoni occurs with much higher frequency in whites than in blacks. After treatment, reversion of hepatosplenic schistosomiasis occurs more frequently in non-whithers. It seems that the resistance of blacks to the hepatosplenic form of schistosomiasis may be related to the glyoxalase system, perhaps associated to another genetic marker. The hepatosplenic schistosomiasis is less frequent in longilineal individuals.

In some areas the hepatosplenic form of schistosomiasis is more frequent in A blood group of ABO sistem.

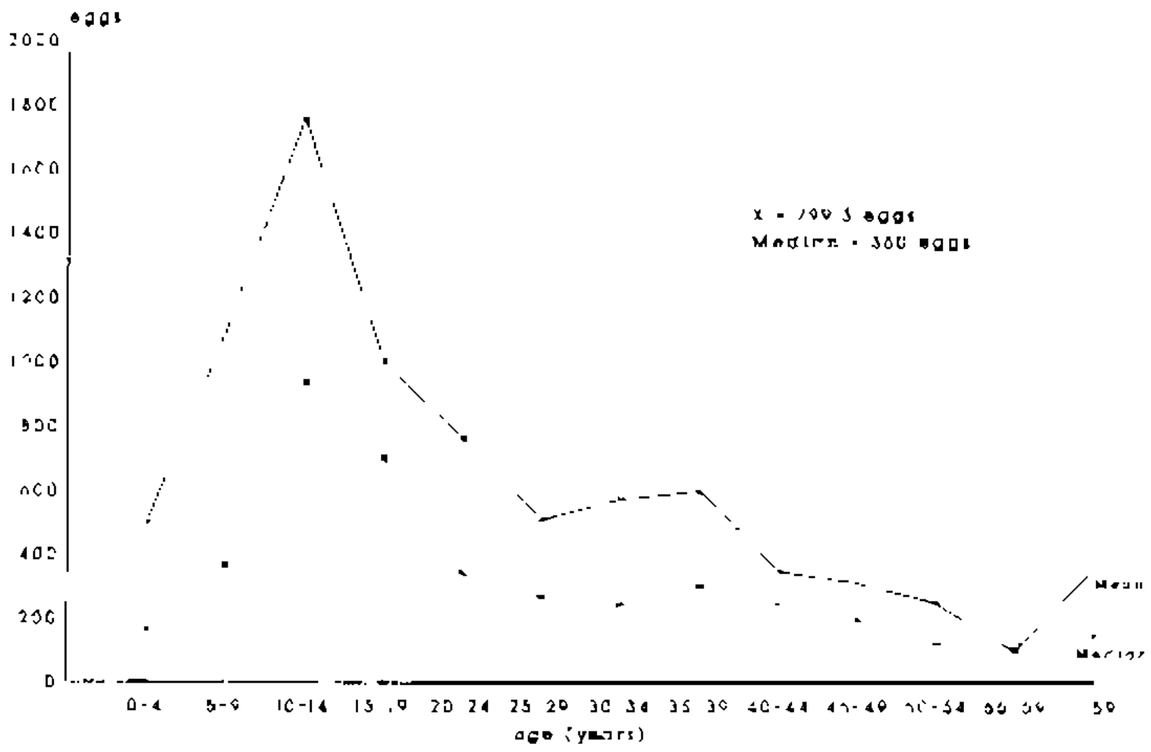
The family heredograms do not suggest a single mendelian inheritance, but probably a multifactorial and possibly poligenic one.

Key words: schistosomiasis mansoni – hepatosplenic form – host factors

The controversy still remains on the relationship between the eggs eliminated with stools, the parasitic load and the development of the hepatosplenic form of schistosomiasis. Although the matter is not part of our presentation we want, however to stress certain aspects. At Caatinga do Moura, some patients, two or four years before developing the hepatosplenomegaly, have shown small quantity of eggs eliminated in the feces and thus continued after the installatation of that clinical form of the disease (Table I). The age groups with the highest egg counts in stools and with hepatosplenic form are coincident (Fig.). Apparently, the hepatosplenics can eliminate more eggs in the feces than the rest of the population (Table II). However, pairing individuals with or without hepatosplenomegaly in an endemic area, according to their age, we have not found differences in the quantity of eggs eliminated by both groups (Table III).

The hepatosplenic form of the schistosomiasis is found more in areas with higher prevalence of the disease (Pessoa & Barros, 1953; Kloetzel, 1963; Abaza et al., 1985). On the other hand, at Brejo do Espírito Santo, we have not found any correlation between the parasitic load and the development of hepatosplenomegaly after a four-years follow up (Table IV).

Such factors suggest, at least, that the high parasitic load is not the only factor determining the severe forms of schistosomiasis.



Schistosoma mansoni egg counts in stools of 904 patients, according to the age, from Brejo do Espírito Santo.

TABLE I

Egg counts before and after the development of the hepatosplenic form of schistosomiasis mansoni, in Caatinga do Moura, 1968 (Prata & Bina, 1968)

No. eggs/g	Before	After
0		1
100 – 500	14	13
600 – 1100	5	5

TABLE II

Egg counts of the hepatosplenic patients compared with the population, from Brejo do Espírito Santo

	No.	Mean	Median
Controls	829	799	360
Hepatosplenics	75	1028	360
		904	

TABLE III

Egg counts in 81 hepatosplenic and 81 controls, matched for age and sex, from Brejo do Espírito Santo

Eggs	Hepatosplenics	Controls
0	6	7
1 – 99	15	14
100 – 499	30	23
500 – 999	10	15
>999	20	22
Mean	952	1060
Median	264	360

TABLE IV

Egg counts in stool as a risk for hepatosplenomegaly four years later, at Brejo do Espírito Santo

Egg counts	Patients	Hepatosplenomegaly
0	254	4 (1.6%)
1 – 99	180	14 (7.7%)
100 – 499	303	17 (5.6%)
500 – 999	137	10 (7.3%)
>999	209	12 (5.7%)
	1083	57

EXPOSURE TO THE RISK OF REINFECTIONS

Hepatosplenic forms are developed only when subjects keep close contact with infection focuses. When they are removed from endemic areas, that clinical form does not develop (Coura, 1975). The severe forms do not evolve if the subjects remain in endemic areas with lowered opportunity of re-infection by continuous use of molluscicides. One may suppose that re-infections would increase parasitic load by breaking the apparent balance between the laying and destruction of eggs in the tissues (Cheever et al., 1977), by worsening the total egg accumulation (Warren, 1972), or by altering the host response regardless of increasing or not of the parasitic load.

In endemic areas, the studies show correlation between contacts with the water, the prevalence of infection (Jordan, 1972) and the amount of eggs expelled in the stools (Costa, 1972). However, the exposure to reinfections does not always lead to an increase in parasitic load. This may even be lost even though the subject keeps exposed to the risks of the infection (Hairston, 1973). People submitted to the same water contact in endemic regions, present different rates of egg elimination in stools. This was shown largely in patients treated and exposed to the same re-infection risks (Butterworth et al., 1985). Some are susceptible to re-infections while others do not get reinfected (Prata et al., 1980). Abel et al. (1991) studying the pedigrees of 269 Caatinga do Moura individuals through segregation analysis conclude that the resistance/susceptibility to infection by *Schistosoma mansoni* are dependent on a major codominant gene.

AGE AND DURATION OF THE DISEASE

The hepatosplenic form is found only after 6 years of age, mostly between 15 and 20

TABLE V

Correlation between clinical forms of schistosomiasis mansoni and race, at Inhaúmas

Clinical forms	Race		
	White	Mullato	Black
Hepatintestinal without liver fibrosis	731 (93.2%)	677 (93.9%)	239 (95.2%)
Hepatintestinal with liver fibrosis	26 (3.3%)	24 (3.3%)	6 (2.4%)
Hepatosplenomegaly	27 (3.4%)	20 (2.8%)	6 (2.4%)
Total	784 (100%)	721 (100%)	251 (100%)

TABLE VI

Correlation between clinical forms of schistosomiasis mansoni and race, at Brejo do Espírito Santo

Clinical forms	Race		
	White	Mullato	Black
Hepatintestinal without liver fibrosis	174 (89.7%)	661 (89.8%)	278 (90.8%)
Hepatintestinal with liver fibrosis	3 (1.5%)	22 (2.9%)	15 (4.9%)
Hepatosplenomegaly	17 (8.8%)	53 (7.2%)	13 (4.2%)
Total	194 (100%)	736 (100%)	306 (100%)

years. It is slowly installed around 4 to 15 years after the initial infection by *Schistosoma mansoni*. It is discussed which one is important the patient's age or only the duration of the disease. At Nova Esperança, where introduction of transmition seems to have been recent, we found only young hepatosplenics, indicating that at that location, adults have not developed the severe form. However, Pessoa & Coutinho (1953) verified severe forms in adults submitted to continous reinfections.

RACE

At least in some parts of Brazil, blacks are more resistant to the development of hepatosplenic forms of schistosomiasis (Cardoso, 1953; Prata & Schroeder, 1967; Pereira, 1979; Coura et al., 1982; Tavares-Neto & Prata, 1990) in spite of acquiring the infection under the same frequency and intensity (Prata & Schroeder, 1967) and living under worse social and economical conditions (Tavares-Neto & Prata, 1990). At Catolândia even excluding the blacks, the frequency of hepatosplenomegaly in whites is three times higher (Tavares-Neto, 1987). At Inhaúmas hepatosplenomegaly is also more common in whites (Table V). At Brejo do Espírito Santo we have seen blacks developing more hepatic fibrosis, and less splenomegaly (Table VI). This suggests that even among black subjects there is difference in the answer to the infection regarding the clinical forms of the disease.

The higher hepatosplenic prevalence in whites reflects in a 'funny way on the surnames, as was found by Tavares-Neto (1987) at Catolândia. The hepatosplenics have less of religious surnames and more of plant and animal surnames. The first kind is more usually adopted by the blacks. The plant and animal surnames are preffered by whites.

Tavares-Neto & Prata (1988) have shown that specific treatment has produced hepatosplenomegaly regression in 10 (47.6%) of 21 non-white patients in comparison to 2 (8.3%) among 24 whites.

Such observations show that racial factors may be related to the susceptibility and resistance to hepatosplenomegaly and to its regression after specific treatment.

OTHER INDICATIONS OF GENETIC INFLUENCE

Familial occurrence – Familial occurence of several hepatosplenics in the same nuclear family has been verified by several workers (Warren, 1973; Conceição & Coura, 1980). Those who work in endemic areas notice that certain families are stigmatized by the frequency of hematemesis. It is not casual the concentration of hepatosplenics within certain families (Conceição & Coura, 1980). As, in general, members of the same family contact to the same contagious focus, it is difficult to segregate what would be due to the environment (Warren, 1973).

Our studies (Tavares-Neto & Prata, 1989a) at Catolândia have shown that out of 265 families, only 72 had one hepatosplenic among their members, and in 38 there were two or more. From these, 8 had 4 or more hepatosplenics. This hepatosplenic concentration in the same familial nucleus is much higher than expected and is statistically highly significative. The concentration of the hepatosplenic form was also high among siblings, among mothers and children, and among fathers and children, but not between, husbands and wives. Comparing with the father, when the mother was hepatosplenic the risk of children contracting the same clinical form was 5 times higher (maternal effect).

The herodogram study of these families does not suggest simple mendelian heredity, but, probably, multifactorial and, possibly, poligenic (Tavares-Neto & Prata, 1989b).

Inbreeding coefficient – At the Catolândia region the inbreeding coefficient for the hepatosplenics was 26.8% while the same coefficient for hepatointestinals was 12.5% (Tavares-neto & Prata, 1989a). Genetic influence is suspected when a certain condition is directly proportional to the inbreeding coefficient (Beiguelman, 1983). That coefficient was higher in whites than in other racial groups. Those who own irrigation lands present high inbreeding coefficient and are mostly whites. The consanguinity increases the likelihood of gene concentration and thus, the exacerbation of the characteristics. Therefore, the high prevalence of hepatosplenic forms in certain irrigation areas, at least in Bahia, should not be assigned only to the high parasitic load related

TABLE VII

Correlation between clinical forms of schistosomiasis mansoni and biotype, at Brejo do Espírito Santo

Clinical forms	Biotype		
	Longilineal	Normolineal	Brevilineal
Hepatintestinal without liver fibrosis	175 (90.7%)	334 (90.5%)	131 (87.9%)
Hepatintestinal with liver fibrosis	10 (5.2%)	13 (3.5%)	1 (0.7%)
Hepatosplenomegaly	8 (4.1%)	22 (6%)	17 (11.4%)
Total	193 (100%)	369 (100%)	149 (100%)

TABLE VIII

Correlation between clinical forms of schistosomiasis mansoni and biotype, at Inhaúmas

Clinical forms	Biotype		
	Longilineal	Normolineal	Brevilineal
Hepatintestinal without liver fibrosis	234 (97.9%)	1116 (93.3%)	212 (88%)
Hepatintestinal with liver fibrosis	2 (0.8%)	41 (3.4%)	16 (6.6%)
Hepatosplenomegaly	3 (1.3%)	39 (3.3%)	13 (5.4%)
Total	239 (100%)	1196 (100%)	241 (100%)

TABLE IX

Correlation between clinical forms and ABO blood groups, at Brejo do Espírito Santo

Clinical forms	Blood groups				
	A	B	O	AB	Total
Hepatintestinal without liver fibrosis	224 (87.8%)	92 (90.2%)	382 (89.4%)	7 (85%)	705
Hepatintestinal with liver fibrosis	11 (4.3%)	4 (3.9%)	11 (2.6%)	1 (5%)	27
Hepatosplenomegaly	20 (7.8%)	6 (5.9%)	34 (8%)	2 (10%)	62
Total	255 (100%)	102 (100%)	427 (100%)	20 (100%)	

to close contact with the water contaminated by cercaria (Prata, 1988).

Biotype – Studying the biotype of 711 patients in relation to the clinical forms of schistosomiasis at Brejo do Espírito Santo we verified that hepatosplenics are more frequent among brevilineal subjects and less frequent among those longilineal (Table VII). We have observed similar results (Prata & Silva, unpublished in 1676 subjects at Inhaumas (Table VIII).

GENETIC MARKERS

Blood groups – Some studies have shown that the hepatosplenic form of schistosomiasis mansoni (Khattab et al., 1968; Camus et al., 1977; Pereira et al., 1979; Tavares-Neto, 1987) as well as the japonic (Wang et al., 1983) may occur more often in subjects of the A blood group, although such association has not been confirmed in other studies (Katz et al., 1967; Pereira et al., 1979; El Masri & Sharfi, 1982). It also has happened at Brejo do Espírito Santo (Table IX).

HLA system – There are studies mentioning correlation between the hepatosplenic form and antigens A1 and B5 of the hystocompatibility system (Abaza et al., 1985; Abdel-Salam et al., 1979). Pereira et al. (1979) has shown no association. However she may have used other antigens. The presence of B5 and B8 antigens was related to intestinal poliposis. The presence of CW2 was related to low response to schistosoma eggs and so to the absence of symptoms (Abdel-Salam et al., 1986). The carriers of BW44-DEN haplotype have predisposition to schistosomotic hepatic fibrosis (Ohta et al., 1982).

Glyoxalase I system – Weimer et al. (1991) have studied the genetic variability in 13 protein systems in 61 hepatosplenic patients and in 61 hepatointestinals. The results have shown that the hepatosplenic incidence is four times higher in GLO*1/GLO*1 homozigotes and three times higher in GLO*1/GLO*2 heterozigotes than in GLO*2/GLO*2 homozigotes.

Insensitivity to phenylthiourea – The frequency of insensitivity to phenylthiourea was similar in the 50 hepatosplenic patients compared the 50 hepatointestinals (Tavares-Neto et al., unpublished).

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