

T CELL-DEPENDENT IMMUNODEPRESSION *IN VIVO* IN *SCHISTOSOMA MANSONI* INFECTED PATIENTS

Maria Imaculada Muniz-Junqueira,
Carlos Eduardo Tosta and Aluizio Prata

T-cell function was evaluated in 29 patients with either hepatointestinal or hepatosplenic schistosomiasis by intradermal tests to recall antigens. Immunodepression was detected in 26% of the subjects with hepatointestinal schistosomiasis and in 50% of those with the hepatosplenic form. Cellular immunodepression was related to worm load and spleen size. This non specific T-cell immunodepression may represent a serious constraint to the elimination of intracellular pathogens both in hepatosplenic or hepatointestinal schistosomiasis.

Key-words: Schistosomiasis. T-cell dependent immunodepression.

In acute schistosomiasis both B-cell¹⁸ and T-cell²⁹ functions are increased. However, during the chronic phase, modulation of the host immune response results in diminution of antibody levels¹⁹ and T-cell function, causing a decrease in granuloma size^{1 5}. Thus, a situation of chronic immunodepression ensues, as shown in experimental models²⁹.

Lymphocyte responses in schistosomiasis have been studied both in human beings^{6 7 11 20 25} and in experimental animal models^{2 16 17 22}. Several studies have demonstrated a depression of lymphocyte blastogenesis towards antigens of *Schistosoma mansoni* eggs^{3 6}. This response, however, is not invariably decreased as showed when cercarial or adult worm antigens^{11 17 20 25}, mitogens or unrelated antigens are used^{2 7 16 22}.

Little is known of the correlation between immunodepression, the clinical presentation of the disease and worm burden. Ellner et al¹⁰ have demonstrated that in hepatointestinal patients with high worm burden the *in vitro* blastogenic response to antigens of adult worms was decreased. On the other hand, patients with the hepatosplenic form showed either an absent or an exacerbated response to antigens of the adult worm, while the response to mitogens and to

streptokinase-streptodornase was normal.

It has been shown that patients with severe schistosomiasis⁸ and those with associated chronic salmonellosis¹³ display depression of delayed hypersensitivity. However, little is known on the degree of immune reactivity of individuals with less severe schistosomiasis, which represents the most frequent population living in endemic areas. A better definition of their T-cell response towards unrelated antigens would help us to understand the immune response of these individuals against microorganisms or vaccines which depend on T-cell immunity.

The present work aimed to evaluate T-cell response to unrelated antigens in patients with the hepatointestinal or hepatosplenic schistosomiasis.

STUDY GROUPS AND METHODS

Twenty nine patients of both sexes, 9 to 43 years old (mean \pm sd = 24.5 \pm 10.0) were studied. Most of them (75%) were white. The diagnosis of schistosomiasis was established on clinical and parasitological grounds. For several years these patients have been followed up clinically and parasitologically. Before being selected for the study they were reexamined and their clinical forms were classified according to the criteria defined by Prata²³. Examination showed no important clinical manifestations or nutritional imbalance.

Eggs of *Schistosoma mansoni* in faeces were detected by the Kato-Katz method¹⁴, and the worm burden was evaluated by the number of eggs per gram of faeces. Worm burden was considered as light when less than 200 eggs/g faeces were found, moderate from 200 to 1000 eggs/g and high when more than 1000 eggs were passing per gram of faeces.

The control group was formed by ten healthy individuals of both sexes, with ages varying from 20 to

Núcleo de Medicina Tropical e Nutrição e Laboratório de Imunologia Celular, Faculdade de Ciências da Saúde, Universidade de Brasília. Brasília, DF, Brasil.

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Present address for correspondence: Dra. Maria Imaculada Muniz-Junqueira, Departamento de Pediatria, Faculdade de Ciências da Saúde, Universidade de Brasília. 70910 Brasília, DF, Brasil.

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50 years old (mean \pm sd = 26.5 \pm 5.0), 70% of them being white.

T-cell response was evaluated by means of intradermal tests, using the following recall antigens: oidiomycin, PPD, streptokinase-streptodornase, trichophytin and vaccinia virus. The later was exclusively used in those individuals showing a scar of smallpox vaccine.

Volumes of 0.1 ml of antigen solution were intradermally injected in the undersurface of the left forearm. Reactions were read 48 hours later and considered as positive when equal or higher than 5 mm in the largest diameter, according to standard techniques²⁷.

The statements of the Helsinki Declaration were strictly followed throughout the investigation.

The results were statistically analysed by the Chi-square test and the Fisher's exact test.

RESULTS

Fifty percent (5/10) of the individuals with hepatosplenic schistosomiasis (HS) and 26% (5/19) of those with hepatointestinal form (HI) presented no response to any of antigens tested. This pattern of response did not occur in any of the 10 normal controls ($p < 0.05$), as showed in Table 1.

Table 1 - Response of hepatointestinal (HI), hepatosplenic (HS) and normal individuals to recall antigens by intradermal test.

Groups	N	Anergy to all antigens		Response to, at least, one antigen	
		N	%	N	%
Normal	10	0	(0)	10	(100)
HI	19	5	(26)	14	(74)
HS	10	5	(50)	5	(50)*

N = number of individuals

* Significantly different from normal individuals ($p < 0.05$) Fisher's Exact Test.

applied in *Schistosoma*-infected patients, only 31 (26%) were positive, while 25 out of 44 tests (57%) applied in control individuals were positive ($p < 0.001$). No statistical difference was found between HS and HI patients, although positive tests were more frequently observed among HI (30%) than is HS individuals (17.5%). Each group gave statistically different results when compared with normal controls (Table 2).

Table 2 - Response of hepatointestinal (HI), hepatosplenic (HS) and normal individuals to recall antigens by intradermal test: a general assessment of positive reactions.

Groups	Total of tests	Response			
		Positive		Negative	
		N	%	N	%
Normal	44	25	(57.0)	19	(43.0)
HI	81	24	(30.0)	57	(70.0)*
HS	40	7	(17.5)	33	(82.5)**

* Significantly different from normal individuals ($p < 0.01$) Chi-Square Test.

** Significantly different from normal individuals ($p < 0.001$) Chi-Square Test.

Subjects with schistosomiasis showed a lower frequency of positive tests for each individual antigen as compared to controls, except for vaccinia antigen. The positivity of schistosomiasis patients was 4% (1/26) with trichophytin, 7% (2/29) with streptokinase-streptodornase, 31% (9/29) with oidiomycin, 45% (13/29) with PPD and 62.5% (5/8) with vaccinia virus. While in normal individuals the following frequency of positive tests was found: 25% (1/4) with trichophytin, 30% (3/10) with streptokinase-streptodornase, 80% (8/10) to oidiomycin, 80% (8/10) to PPD and 50% (5/10) to vaccinia virus.

The frequency of positive tests correlated inversely to worm burden, both in HS and HI patients. From a total of 81 intradermal tests applied in the HI group, 38% (10/26) were positive in those individuals with a light worm burden, 29% (10/34) in those with a moderate load, and only 19% (4/21) in patients with high worm load. While 30% (6/20) of those from the HS group not passing *S. mansoni*-eggs gave positive intradermal tests, this test was positive in only 5% (1/20) of the HS individuals presenting eggs in faeces, whereas normal individuals gave 57% (25/44) positivity (Table 3).

From the total of the 121 intradermal tests

Table 3 - Response of intradermal test to recall antigens in relation to *S. mansoni* load in patients with hepatointestinal (HI) or hepatosplenic (HS) schistosomiasis.

Groups	Worm Load	N	Response			
			Positive		Negative	
			N	%	N	%
Normal	absent	10	25/44	(57)	19/44	(43)
	light	6	10/26	(38)	16/26	(62)
HI	moderate	8	10/34	(29)	24/34	(71)*
	high	5	4/21	(19)	17/21	(81)**
HS	without egg in faeces	5	6/2	(30)	14/20	(70)*
	with egg in faeces	5	1/20	(5)	19/20	(95)**

* Significantly different from normal ($p < 0.05$) Chi-Square Test.

** Significantly different from normal ($p < 0.01$) Chi-Square Test.

A complete unresponsiveness to all antigens was detected in 4 out of 5 HS patients passing *S. mansoni*-eggs, and in only one with no eggs in faeces. This latter individual had a palpable spleen 9 cm below the left costal edge.

On the other hand, a complete unresponsiveness to all intradermal tests applied occurred in 3 out of 4 patients with the spleen larger than 6 cm, but in only 2 out of 6 whose spleen was smaller than 6 cm. These two patients also showed the highest worm load of all the HS patients (984 and 672 eggs/g). Moreover, the only non-anegetic patients with a spleen larger than 6 cm did not show *S. mansoni*-eggs in faeces at the moment of the examination.

DISCUSSION

Cellular immunodepression to *Schistosoma mansoni*-egg antigens during infection may benefit the host, since the granulomatous reaction to the eggs plays a crucial role in the pathogenesis of schistosomiasis.²⁹ However, the development of non-specific cellular immunodepression may represent a serious constraint to the elimination of intracellular pathogens during schistosomiasis.^{9 12}

In our study, 26% of hepatointestinal and 50% of hepatosplenic patients presented T-dependent immunodepression. Similar findings were obtained by Coutinho et al⁸ and Higashi¹³ in hepatosplenic patients. However, our data show that individuals even with mild infection may present cellular immunodepression. It can be postulated that this non-specific t-cell immu-

nodepression may make difficult the elimination of pathogens such as salmonellas, since this response is important to immunity to this bacteria^{4 15}.

We show that patients with schistosomiasis presented less positive response to the antigens tested, except for vaccinia virus. However, there was a gradation of positive responses, varying from 4% with trichophytin to 62.5% to vaccinia virus. This indicates that T-cell immunodepression is not an all or none phenomenon. This diversity of response may occur due to the frequent individual variability of host-parasite relationships in schistosomiasis, which depend on the duration of infection, worm burden, clinical form, and the individual response of each patient to the pathogen. This results in different degrees of involvement of the immune system of the host.

Our results show that T-cell immunodepression was related to *S. mansoni* load. This indicates that unspecific cellular immunodepression depends on factors related to worm or egg antigens. Accordingly, Ellner et al¹⁰ have demonstrated a decreased blastogenic response in vitro in schistosomiasis patients with high-level infection. In fact Todd et al²⁸ and Ottesen et al²¹ have presented evidence of immunodepression in vitro related to humoral factors, possibly antigens or immunocomplexes, present in the sera of schistosomiasis patients.

The verification that 50% of the hepatosplenic patients did not present *S. mansoni*-eggs in their faeces, and that none of them presented high worm burden suggest that besides worm and eggs antigens, other factors may play a role in the immunodepression associated to schistosomiasis. The inverse relationship between T-cell responsiveness and size spleen indicates that immune response is more altered in those patients presenting more severe anatomical and functional involvement by the infection.

Although the factors responsible for immunodepression in schistosomiasis are not completely determined it has been suggested that both suppressor cells²⁶, or adherent phagocytic cells²⁴ may play a role. Our data suggest that immunodepression in schistosomiasis depend on the degree of clinical involvement and, probably, on the amount of antigen released by the parasite.

RESUMO

A imunidade celular foi avaliada em 29 pacientes com as formas hepatoesplênica ou hepatointestinal, da esquistossomose mansoni, através de testes intradérmicos com antígenos não relacionados ao *Schistosoma*. Imunodepressão foi detectada em 26% dos

pacientes com a forma hepatointestinal e em 50% daqueles com a forma hepatoesplênica. A imunodepressão celular foi relacionada com a carga parasitária e o tamanho do baço. Esta imunodepressão celular pode dificultar a eliminação de patógenos intracelulares tanto na forma hepatoesplênica quanto na forma hepatointestinal da esquistossomose.

Palavras-chaves: Esquistossomose. Imunodepressão celular.

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