SPECIFIC TREATMENT OF HEPATOSPLENIC SCHISTOSOMIASIS CAN INCREASE T-LYMPHOCYTE REACTIVITY

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It has been recognized that Schistosoma mansoni infection causes depression of T-cell responsiveness. In this study we have evaluated whether immunodepression associated to schistosomiasis could be reverted by specific treatment. T-cell immune response was assessed by means of intradermal tests using recall antigens in a group of 22 patients with hepatosplenic schistosomiasis, one year after treatment with oxamnique and compared with a group of untreated hepatosplenic patients. Only 27% of treated patients presented complete anergy to all tested antigens, in marked contrast to 80% unresponsiveness showed by hepatosplenic patients without treatment. Although most of the treated individuals showed some response to the tested antigens, in some individuals this unresponsiveness still persisted after treatment. Anergy was not found in any normal individual of the control group. It was concluded that Schistosoma mansoni infected patients may recover their normal immune responsiveness after the elimination of the worm by treatment.

Key-words: Immunodepression. Schistosomiasis. Oxamnique.

It is well established that infection by Schistosoma mansoni results in a depressed function of T-lymphocytes\(^6\). This immunodepression may be both specific\(^4\) or unrelated to the antigens of schistosoma worm\(^10\) 11 18. The non-specific immunodepression may represent a serious constraint to the elimination of intracellular pathogens in these patients\(^13\).

T-lymphocyte immunodepression in patients with schistosomiasis has been related to the worm burden\(^18\) and can be induced by the administration of worm membrane preparation to non-infected mice\(^16\).

It is therefore possible that T-lymphocyte immunodepression to unrelated antigens in Schistosoma-infected patients may be reverted by the elimination of the worm by means of specific therapy.

This work aimed to evaluate in vivo T-lymphocyte response to unrelated antigens in patients with hepatosplenic schistosomiasis after the elimination of the worm by specific therapy.

MATERIAL AND METHODS

The ethical rules of the Helsinki Declaration\(^12\) were strictly followed throughout this investigation.

Twenty two patients of both sexes and 35±14 years old with hepatosplenic schistosomiasis were studied. Most of them (55%) were Caucasians. All patients had been previously treated with a single oral dose of 15 mg/kg of oxamnique.

The diagnosis of schistosomiasis was previously established on clinical and parasitological grounds. Eggs of Schistosoma mansoni were detected in faeces by the Kato-Katz method\(^14\). Parasitological assessment of cure was performed after treatment, by the absence of S. mansoni eggs in at least three examination of the faeces. The clinical criteria for the diagnosis of hepatosplenic schistosomiasis were described by Prata\(^15\). Physical examination showed no signs of clinical decompensation or nutritional imbalance. Another three patients, not belonging to the previous group and who had been previously splenectomized, were also treated with oxamnique and submitted to the tests. They also did not show any S. mansoni-eggs in faeces.

The positive control group was formed by five female, 21±8 years old patients with hepatosplenic schistosomiasis. All of them were passing S. mansoni-eggs in faeces. Ten healthy individuals, of both sexes, 26±5 years old, 70% of them Caucasians, were considered as the negative control group.

T-lymphocyte function was evaluated by intradermal tests, using the recall antigens candidin, PPD, streptokinase-streptodornase, trichophytin and vaccinia virus (Allergofar). The later was exclusively used in those individuals showing a scar of smallpox vaccine. One tenth of ml of antigen solution was intradermally injected in the undersurface of the left forearm. Induration was read 48 hours later, and...
considered as positive when the largest diameter was equal or higher than 5 mm.

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

RESULTS

Only six out of 22 schistosomiasis patients without *S. mansoni* eggs in faeces (27%) showed a complete unresponsiveness to all applied intradermal antigens, while 4 out of 5 patients still passing eggs showed anergy. This difference was statistically significant (p < 0.05). However, both groups of schistosomiasis individuals showed a higher frequency of anergic tests, when compared to those of the normal control group, where no anergic individual was found (Table 1).

Table 1 – Response of individuals with active hepatosplenic schistosomiasis (HS), of previously treated HS patients and of normal individuals to recall antigens by intradermal tests.

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Anergy to all applied antigens number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td>Active HS</td>
<td>5</td>
<td>4/5*</td>
<td>80</td>
</tr>
<tr>
<td>Treated HS</td>
<td>22</td>
<td>6/22±/**</td>
<td>27</td>
</tr>
</tbody>
</table>
- *Significantly different from normal group (p<0.05). Fisher's Exact Test.
- **Significantly different from active HS group (p<0.05). Chi-square test.

Twenty one out of the 105 intradermal tests applied in the schistosomiasis group without worm were positive (20%), whereas only one test out of 20 (5%) showed positivity in the group presenting worms. However, both groups showed a significantly decreased number of positive responses when compared with those of normal individuals (57%) (Table 2).

Table 2 – Positivity of the response to recall antigens by intradermal tests of patients with active hepatosplenic (HS) schistosomiasis, of previously treated HS patients and normal individuals.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Positivity of response N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>25/44</td>
<td>57</td>
</tr>
<tr>
<td>Active HS</td>
<td>1/20</td>
<td>5*</td>
</tr>
<tr>
<td>Treated HS</td>
<td>21/105</td>
<td>20*</td>
</tr>
</tbody>
</table>
- *Significantly different from normal group (p<0.05). Chi-square Test.

None of the three splenectomized patients showed anergy and six out of the 15 tests applied (40%) showed positivity.

DISCUSSION

Schistosoma mansoni-infected patients may present T-lymphocyte-dependent immunodepression and this could make difficult the elimination of intracellular pathogens as observed in prolonged septicaemic salmonellosis associated with schistosomiasis. The immunodepression is related to the worm burden. Thus, it can be postulated that the elimination of *S. mansoni* by means of specific therapy would help recovering normal immune responsiveness.

Our data showed that hepatosplenic individuals, considered to be cured by chemotherapy, presented a lower degree of T-cell immunodepression than those who were actively passing *S. mansoni* eggs in faeces. In support to our data are the observations of Abdel-Salam et al and Barsoum et al who showed increased in vitro proliferative responses of lymphocytes to mitogens or antigens, after specific treatment of Schistosoma-infected patients. It has also been demonstrated in mice infected with *S. mansoni* or *S. haematobium* an increased reactivity of lymphocytes after treatment with praziquantel.

Our results also indicated that the recovery of T-cell reactivity was not complete in some treated individuals. Although the reasons for that are not known, it is possible to speculate that it could be related to the degree of previous involvement of the immune system due either to the duration of the infection, the worm burden or the peculiar response of each individual. In fact, Tawfik et al have showed in mice that the duration of infection prior to treatment was a determining factor in the subsequent expression of immunoreactivity. Butterworth et al have also showed in *S. mansoni*-infected patients that the resistance to reinfection after specific therapy depended on the duration of previous infection.

The low frequency of individuals with T-lymphocyte immunodepression amongst treated patients points to the possibility that factors related to the presence of *S. mansoni* may play a causal role. In fact, it has been showed that injections of worm membrane preparation induces immunodepression in normal mice and, in patients, this immunodepression is related to the worm burden. However, other factors can also be implicated in the development of this immunodepression, since the elimination of the worm is not enough to completely revert immunodepression. It is possible that factors related to the alterations of the structure and functions of the liver and spleen during the infection, which can persist after treatment may play a role in this immunodepression. In fact, our limited observation of three patients previously splenectomized and treated with oxamniquine showed that none of them presented with anergy to all antigens, and the number of positive responses to intradermal tests was similar to that of the normal individuals. Besides, it has been showed that immunodepression is related to the spleen size.

The specific treatment may benefit Schistosoma-infected patients both by the elimination of the worm, and by the reversion of the immunodepression. It can also decrease the spleen size, which may be related with immunodepression.
RESUMO

Tem sido observado que infecção por Schistosoma mansoni pode causar imunodepressão celular. Neste trabalho foi avaliado se a imunodepressão associada à esquistossomose pode ser revertida pelo tratamento específico. A resposta imune celular foi determinada através de testes cutâneos de hipersensibilidade retardada em 22 pacientes com a forma hepatosplênica da esquistossomose um ano após tratamento com oxamnique e comparado com aquele observada em um grupo de pacientes hepatosplênicos não tratados. Somente 27% destes pacientes apresentaram alergia a todos os antígenos testados, em contraste com 80% de indivíduos anêrgicos observados entre aqueles não tratados. Embora a maioria dos indivíduos tratados tenha mostrado algum grau de resposta aos antígenos testados, alguns indivíduos permaneceram anêrgicos após o tratamento específico. Anergia a todos os antígenos aplicados não foi observada em nenhum dos indivíduos normais. Nossos dados indicam que pacientes esquistossômicos podem recuperar sua reatividade imune após a eliminação do verme pelo tratamento específico.


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REFERENCES