

Correspondence

Association between Serum Cytokine Profiles and Schistosomiasis-Related Hepatic Fibrosis: Infection by *Schistosoma japonicum* versus *S. mansoni*

To the Editor—In the 1 August 2005 issue of the *Journal*, Coutinho et al. described, in patients infected by *Schistosoma japonicum*, a correlation between the levels of certain cytokines and the presence of hepatic fibrosis (HF) [1]: they found that the levels of both interleukin (IL)-1 and IL-6 were higher in patients with HF than in patients without HF, and they also reported that the presence of HF was negatively correlated with body-mass index. We found these results to be particularly interesting, because we have noted a similar correlation between HF and immunological parameters.

We recently reported a relationship between anti-soluble egg antigen (anti-SEA)-isotype antibody responses and portal hypertension (PH) in *Schistosoma mansoni*-infected patients in Saint Louis, Senegal [2]. This hyperendemic situation is noteworthy in that the illness emerged after a recent change in the ecosystem—a dam was constructed on the Senegal River in 1986, and the first cases of schis-

tosomiasis were diagnosed in 1988. The disease was severe and rapidly progressive, with the first cases of PH being observed in 1994 [3].

Using hepatic sonography and gastric fibroscopy, we have screened for HF in a cohort of 142 *S. mansoni*-infected patients; patients with HF were classified as belonging to 1 of 3 categories based 3 stages of pathology: (1) those who were free of HF (no morbidity—i.e., clinical and hepatic ultrasound findings were normal); (2) those in whom hepatic ultrasound findings were abnormal but in whom gastric fibroscopy showed no signs of PH (moderate morbidity); and (3) those in whom gastric fibroscopy showed esophageal varices (severe morbidity). We found that the presence of PH—and, therefore, of HF—correlated positively with levels of anti-SEA IgG4, IgA, and IgE [2]. We also measured serum levels of pro- and anti-inflammatory factors—soluble intercellular cell-adhesion molecule-1, soluble tumor necrosis factor receptor-1 and -2, interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and IL-10—in the same patients, to determine whether HF was associated with a particular inflammatory profile. As shown in table 1, levels of IL-

10 were higher in patients with stage 3 disease than in patients with either stage 1 disease or stage 2 disease, whereas levels of IFN- γ were lowest in patients with stage 2 disease.

This correlation between the clinical stage of the disease and the serum level of IL-10 was independent of age, sex, or severity of infection (as determined on the basis of *S. mansoni* egg counts in stool samples). High levels of an anti-inflammatory cytokine, such as IL-10, during the advanced stage of the disease may be linked to PH itself. Indeed, inflammation triggered by PH could lead to the secretion of anti-inflammatory cytokines, and these elevated levels of IL-10 would therefore reflect an attempt to dampen the inflammatory reaction. Other studies have also suggested a link between high levels of IL-10 and the severity of parasitic infections; for example, Perkins et al. [4] and Ho et al. [5] have reported that severe malaria is associated with elevated levels of IL-10.

Our findings show that the inflammatory balance is altered in *S. mansoni*-infected patients who have advanced HF. The differences between stages 2 (moderate HF) and 3 (severe HF) of the disease

Table 1. Levels of pro- and anti-inflammatory factors, for different stages of pathology of hepatic fibrosis.

Cytokine	Stage 1 (n = 28)	P^a		P^a	
		(stage 1 vs. stage 2)	Stage 2 (n = 10)	(stage 2 vs. stage 3)	Stage 3 (n = 10)
sTNFR-1, pg/mL	683 (531–1550)	.264	669 (489–998)	.241	744 (532–2128)
sTNFR-2, pg/mL	2264 (1403–6781)	.208	2748 (1709–7174)	.031	1945 (1214–2953)
TNF- α , pg/mL	238 (0–921)	.113	126 (0–471)	.264	177 (22–2452)
sICAM-1, ng/mL	826 (62–2426)	.281	738 (32–1739)	.157	604 (356–1142)
IL-10, pg/mL	141 (0–2914)	.339	140 (0–344)	.017	359 (79–3162)
IFN- γ , IU/mL	2.15 (0–6.2)	.022	0 (0–5.4)	.026	2 (0–10)

NOTE. Data are median (range) of values, unless otherwise indicated. IFN, interferon; IL, interleukin; sICAM, soluble intercellular cell-adhesion molecule; sTNFR, soluble tumor necrosis factor receptor; TNF, tumor necrosis factor.

^a $P < .05$ (nonparametric Mann-Whitney test) was considered to be statistically significant; these values are in boldface type. A statistically significant difference ($P = .031$) also was found between stages 1 and 3, for both IL-10 and sICAM-1.

could serve as a means by which to monitor disease progression, without the need for invasive examinations (e.g., gastric fibroscopy to detect esophageal varices). Early detection of a change from a pro- to an anti-inflammatory cytokine profile could serve as a way to identify a high-risk population of patients who require closer clinical and biological monitoring. In the same way that antibody responses vary between stages 2 and 3 of the disease [1], the inflammatory profile changes as the disease progresses, suggesting that advanced stage of the disease are accompanied by an accelerated immune reaction. The concomitant increase in levels of IFN- γ during the later stage of the disease (i.e., stage 3 vs. stage 2) (table 1) implies the presence of a mechanism of this type.

Finally, the fact that, despite the difference in the parasite species studied (*S. japonicum* vs. *S. mansoni*), our results are similar to those of Coutinho et al. suggests that there is a common pathophysiological mechanism governing the onset and regulation of HF in patients with schistosomiasis.

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References

1. Coutinho HM, McGarvey ST, Acosta LP, et al. Nutritional status and serum cytokine profiles in children, adolescents, and young adults with *Schistosoma japonicum*-associated hepatic fibrosis, in Leyte, Philippines. *J Infect Dis* **2005**; *192*: 528–36.
2. Bonnard P, Remoué F, Schacht AM, et al. Specific isotype immune response in the diagnosis of human schistosomiasis. *Am J Trop Med Hyg* **2004**; *71*:202–5.
3. Stelma FE, Talla I, Verle P, Niang M, Gryseels B. Morbidity due to heavy *Schistosoma mansoni* infections in a recently established focus in northern Senegal. *Am J Trop Med Hyg* **1994**; *50*:575–9.
4. Perkins DJ, Weinberg JB, Kremsner PG. Reduced interleukin-12 and transforming growth factor- β 1 in severe childhood malaria: rela-

tionship of cytokine balance with disease severity. *J Infect Dis* **2000**; *182*:988–92.

5. Ho M, Sexton MM, Tongtawe P, Looareesuwan S, Suntharasamai P, Webster HK. Interleukin-10 inhibits tumor necrosis factor production but not antigen-specific lymphoproliferation in acute *Plasmodium falciparum* malaria. *J Infect Dis* **1995**; *172*:838–44.

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Reply to Bonnard et al.

To the Editor—It is indeed interesting that, in their study in Senegal, Bonnard et al. [1] found elevated serum levels of interleukin (IL)–10 in patients with severe morbidity due to chronic *Schistosoma mansoni* infection—and that this finding was independent of age, sex, or *S. mansoni* egg count. These results are similar to the findings that my colleagues and I had reported in our article in the *Journal* [2], despite the following differences in the 2 studies' populations and designs: (1) in the study by Bonnard et al., participants were recruited at a local health center, whereas our study was community based; (2) the age range in the study by Bonnard et al. was 11–80 years, versus 7–30 years in our study; (3) current schistosomiasis infection was not a requirement for participation in the study by Bonnard et al. if pathology as detected by ultrasonography or endoscopy was present, whereas in our study it was a requirement for all participants; and (4) the 2 studies used different systems for classification of hepatic fibrosis (HF).

It seems plausible that the immunoregulatory mechanism involved in the development of HF is similar across species. The idea of using noninvasive, immunologic screening tools to facilitate the detection of severe HF and/or associated morbidity is interesting. However, a few issues should be discussed in this regard. First, there is no evidence for a “change

from a pro- to an anti-inflammatory cytokine profile” during the development of severe HF. On the contrary, as mentioned by Bonnard et al., as well as in the Discussion section of our article [2], the increased levels of serum IL-10 that are associated with severe HF likely reflect an attempt to dampen increased levels of proinflammatory cytokines. In line with this hypothesis, we found that both the level of IL-1 and the percentage of individuals with detectable levels of IL-6 were increased in subjects with severe HF [2]. Other studies have found increased levels of a proinflammatory cytokine, tumor necrosis factor (TNF)– α , and its receptor, soluble TNF receptor (sTNFR)–1, in individuals with severe hepatic morbidity [2–5]. In contrast, Bonnard et al. found decreased levels of sTNFR-2 in subjects with severe morbidity—and, with progression of morbidity, a decrease, followed by an increase, in levels of interferon (IFN)– γ .

Second, the determination of which cutoff values for levels of IL-10 should be used to discriminate between different stages of hepatic morbidity may be difficult. Even if studies with large numbers of individuals were used to determine these cutoff values, coinfection with other pathogens could interfere with their reliability. Serum IL-10 is likely not specific enough to qualify as a marker for schistosomiasis-associated hepatic morbidity. Levels of cytokines produced in response to specific schistosome antigens could be used instead, to overcome the confounding effects of coinfection with other pathogens; however, such an assay is likely to be too expensive to have public-health utility in the developing world. Another issue concerns the possible influence of genetic polymorphisms in relation to cytokine responses. Polymorphisms in the IFN- γ receptor gene have been found that may be responsible for the susceptibility of certain individuals to severe HF [6]. Several IL-10 receptor gene polymorphisms may also be of biological significance [7], but their role in the de-

velopment of schistosomiasis-associated HF is currently unknown. These polymorphisms could predispose to development of HF, which would further limit the suitability of serum IL-10 as a marker for hepatic morbidity.

Finally, Bonnard et al. have described other immunologic markers that are specific for schistosomiasis [8] and may be more suitable as markers for disease progression.

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References

1. Bonnard P, Remoué F, Schacht A-M, Pialoux G, Riveau G. Serum cytokine profiles associated with schistosomiasis hepatic fibrosis: similarities between *Schistosoma japonicum*-infected patients in Leyte, Philippines, and *S. mansoni*-infected patients in Richard Toll, Senegal [letter]. *J Infect Dis* **2006**;193:748–9 (in this issue).
2. Coutinho HM, McGarvey ST, Acosta LP, et al. Nutritional status and serum cytokine profiles in children, adolescents, and young adults with *Schistosoma japonicum*-associated hepatic fibrosis, in Leyte, Philippines. *J Infect Dis* **2005**;192:528–36.
3. Henri S, Chevillard C, Mergani A, et al. Cytokine regulation of periportal fibrosis in humans infected with *Schistosoma mansoni*: IFN-gamma is associated with protection against fibrosis and TNF-alpha with aggravation of disease. *J Immunol* **2002**;169:929–36.
4. Booth M, Mwatha JK, Joseph S, et al. Periportal fibrosis in human *Schistosoma mansoni* infection is associated with low IL-10, low IFN-gamma, high TNF-alpha, or low RANTES, depending on age and gender. *J Immunol* **2004**;172:1295–303.
5. Mwatha JK, Kimani G, Kamau T, et al. High levels of TNE, soluble TNF receptors, soluble ICAM-1, and IFN-gamma, but low levels of IL-5, are associated with hepatosplenic disease in human schistosomiasis mansoni. *J Immunol* **1998**;160:1992–9.
6. Dessein AJ, Hillaire D, Elwali NE, et al. Severe hepatic fibrosis in *Schistosoma mansoni* infection is controlled by a major locus that is closely linked to the interferon-gamma receptor gene. *Am J Hum Genet* **1999**;65:709–21.
7. Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* **2003**;55:241–69.
8. Bonnard P, Remoué F, Schacht AM, et al. Specific isotype immune response in the diagnosis

of human schistosomiasis pathology? *Am J Trop Med Hyg* **2004**;71:202–5.

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