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Editorial

A retrospective study of schistosomiasis-associated pulmonary hypertension from an endemic area in Brazil

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Schistosomiasis is a parasitic disease caused by trematode flatworms of the genus *Schistosoma* [1]. Schistosomiasis is the third most prevalent endemic parasitic disease and the most common parasitic disease associated with pulmonary hypertension in the world [2]. An estimated 240 million people are infected and 800 million at risk for infection. Despite its clinical importance, schistosomiasis continues to be a global public health problem in the developing world, and is considered a neglected tropical disease.

Schistosomiasis has two phases, acute and chronic. Acute symptoms start ~50 days after exposure, characterized by fever, abdominal pain and constitutional symptoms [3]. In this phase the inflammatory response is characteristically a T helper 1 (Th1) cell response. After the parasite starts laying eggs, chronic disease begins with variable presentation, with forms including hepatointestinal, hepatosplenic, pulmonary arterial hypertension (PAH), glomerulonephritis and neuroschistosomiasis [1]. The chronic phase is characterized by a Th2 cell response, including the cytokines IL4, IL5, IL10, and IL13 [2,4].

PAH is a rare disease, characterized by increased pressure in the pulmonary circulation and right ventricular overload [5]. *Schistosoma*-associated PAH is classified among the World Health Organization (WHO) Group 1 PAH, and its pathophysiology seems similar to other etiologies of this group including idiopathic, heritable, HIV and autoimmune forms.

Schistosoma-associated PAH is a complication of hepatosplenic schistosomiasis, as hepatic fibrosis and portal hypertension leads to opening of portocaval shunts and embolization of *Schistosoma* eggs to the pulmonary vasculature. The impacted eggs stimulate an immunological reaction leading to the development of granuloma, and vascular remodeling. The pathophysiology of *Schistosoma*-PAH is still poorly understood: vascular obstruction by the eggs does not account for all changes observed. It is likely that the host immune system contribues to the vascular disease, as an apparent unintended side effect. Among those chronically infected, ~10% develop hepatosplenic disease and of these ~8 to 10% develop PAH [2].

There is scarce information regarding the natural history of schistosomiasis-PAH (Sch-PAH). In 2010, Fernandes *et al* reported the outcomes of a retrospective cohort of Sch-PAH patients, and reported overall survival rates at 1, 2, and 3 years of 95.1%, 95.1% and 85.9%, even in the absence of PAH-specific therapy [6]. The subjects in this series, from a referral center in Sao Paulo, were likely migrants from endemic areas and now living in an urban area nonendemic for schistosomiasis. Retrospective series have shown Sch-PAH patients treated with conventional vasodilator therapy have clinical benefit [7,8].

The retrospective study by Roncal *et al* [9] describes clinical factors and outcomes of 68 patients with Sch-PAH diagnosed between 2004 and 2010 at a center in Pernambuco, Brazil, a state where schistosomiasis is endemic. The authors compared their results to survival curves predicted by two PAH registry equations: one from the National Institutes of Health (NIH), designed to estimate prognosis in primary pulmonary hypertension; and the other from the Pulmonary Hypertension Connection (PHC), modified to include survival of Group I PAH with modern therapy [10]. Follow-up was complete in over 95% of cases. The overall survival was nearly 62%, with a median of 74 months. Survival at 1, 3 and 5 years was 92%, 75% and 51%, respectively, which is somewhat worse than that from the Fernandes study [6]. The PHC more accurately predicted the survival curve, while NIH underestimated all survival rates, a finding similar to other modern series of group I PAH [11].

The authors compared clinical variables and outcomes between groups with two different WHO functional classes (FC), I/II (more mild symptoms) *versus* III/IV (more severe symptoms). As expected, those with worse FC had shorter 6-min walk distance and higher pulmonary arterial pressure. Similarly, higher pulmonary vascular resistance and lower cardiac index were found in the worse FC group. Nevertheless, survival rates did not significantly differ, although this comparison was likely underpowered. Surprisingly, a decrease in mean pulmonary artery pressure correlated with increased risk of death, and was an independent prognostic factor. This study also corroborated prior reports that patients with schistosomiasis-associated PAH are less likely to have acute vasodilator responsiveness than those with other forms of PAH [6].

The study enriches the current knowledge about the survival and risk factors for death of Sch-PAH patients, as it retrospectively analyzed a relatively large cohort of patients living in an endemic area in Brazil. The use of two different equations for predicting prognosis also identified more accurate predictors of survival, along with univariate and multivariate statistical analysis to identify and estimate risk factors.

Limitations of the study, acknowledged by the authors, include a retrospective approach, which can be biased by those included in the series, and the accuracy of the data. For example, it was not clear which of the patients were treated for PAH by vasodilator therapy, which can clearly affect outcomes. There was no control group, with either hepatosplenic disease or other WHO Group 1 forms of PAH. The authors

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could not assess if the patients had ongoing *Schistosoma* infection, if they were only exposed earlier in life, if they were reinfected during follow up, or if they received anti-helmenthic therapy: considering patients in this series live in an endemic area, there is a substantial risk patients could be re-infected and require additional anti-helminthic treatment.

We suggest the ideal next step in studying Sch-PAH would be a prospective observation cohort study, ideally done across multiple centers such as those in both endemic and non-endemic regions, inclusive of both incident and prevalent cases. As suggested by the data here, there are likely differences in presentation and outcome between endemic and non-endemic regions. Appropriate control groups would include subjects with hepatosplenic disease without PAH, and other forms of PAH. Prospective collection and analysis of biomarkers would allow identification of potential mechanisms that contribute to the pathophysiology of PAH due to schistosomiasis infection, and factors that impact clinical outcome. In this manner, targeted therapies for Sch-PAH can be developed, beyond vasodilator therapy which is the current mainstay of treatment. Future treatments may also extend to other forms of inflammatory PAH, including that due to HIV infection or autoimmune diseases.

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