Progress in Respiratory Research 41

Pulmonary Vascular Disorders

Bearbeitet von
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ISBN 978 3 8055 9914 6
Gewicht: 1090 g

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Schistosomiasis and Pulmonary Hypertension

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Abstract
Schistosomiasis is the third leading parasitic disease in the world. It is present in 74 countries, infecting 200 million people. Each year 280,000 patients die because of the disease. One of its most severe complications is pulmonary arterial hypertension (PAH). Previous studies have shown that 5% of patients with hepatosplenic schistosomiasis develop PAH. It is believed today that the most prevalent cause worldwide of PAH is schistosomiasis. Specifics about schistosomiasis-associated PAH including epidemiological data, mechanisms of the disease, clinical and hemodynamic features, and modalities of treatment will be reviewed in this chapter.

Geographical and Epidemiological Aspects of Schistosomiasis and Schistosomiasis-Associated Pulmonary Hypertension

Schistosomiasis is one of the most prevalent chronic infectious diseases in the world, and is the third-leading endemic parasitic disease known following malaria and amebiasis [1]. According to the World Health Organization (WHO), there are 200 million patients infected worldwide, 120 million symptomatic patients, and 20 million with severe illness manifestations. The disease is responsible for 11,000 deaths and 1.7 million disability-adjusted life-years lost per year [2]. It is an infection highly related to poverty and lack of basic sanitation, and the main regions of the world afflicted by it are sub-Saharan Africa, China, Southeast Asia, and some areas of Latin America, particularly in Brazil). However, recent reports of schistosomiasis in nonendemic areas, basically due to migration and travel, have renewed the interest in the disease by the global medical community [3].

The global magnitude of schistosomiasis has led to several attempts of epidemic control worldwide, such as the Schistosomiasis Control Initiative. The Schistosomiasis Control Initiative, which has been implemented in some African countries, is a collaborative program focused on morbidity control that is supported by national health and education ministries and the Imperial College London [4]. Similar efforts are pursued by the Special Program for Research and Training in Tropical Diseases of the United Nations Development Program, the World Bank, and the WHO. These programs are of major importance in decreasing the morbidity and mortality associated with schistosomiasis [3].

The first description of the disease was in 1852 by Theodor Bilharz [5]. During an autopsy in Cairo, Egypt, he identified a unique worm in the mesenteric veins of a patient and first described it as bilharziasis, which would later be known as schistosomiasis. Despite the fact that the gastrointestinal and genitourinary tracts were the main systems afflicted, multiple organs have been described as targets of the disease since then. Specifically concerning the respiratory system, in 1932 S. Azmy Pasha [6] first described the most significant and severe form of pulmonary involvement: pulmonary hypertension associated with schistosomiasis (Sch-PH). He described 2 cases of patients with hepatosplenic schistosomiasis with secondary cor pulmonale, and found in the necropsy of these patients remarkable dilations in the pulmonary arteries. One of them also presented with schistosoma eggs in the pulmonary circulation and exuberant granulomatous formations and obliterative arteritis. As times goes by, the relevance of Sch-PH has been progressively acknowledged, mainly in the setting of pulmonary hypertension (PH) and its possible etiologies. It is believed that about 5% of patients diagnosed with hepatosplenic schistosomiasis mansoni may also present with PH [7], suggesting that Sch-PH is potentially the most prevalent cause of PH worldwide.
The importance of Sch-PH might be even greater in regions where schistosomiasis is endemic. Indeed, it is estimated that up to 30% of all PH patients followed at reference centers in Brazil have pulmonary arterial hypertension associated with schistosomiasis (Sch-PAH) [8]. In the updated classification of pulmonary arterial hypertension (PAH) [9], following better understanding of the mechanisms involved in Sch-PAH as well as its hemodynamic features, Sch-PAH has been reclassified within Group I (PAH), the one that raises the most interest in the area as well as the most researched of all five groups.

The Parasite Life-Cycle: Pathology and Immunology of the Infection

Schistosomiasis is caused by a group of parasite trematode worms of the Schistosomatidae family (derived from the Greek word for ‘fissure’ and named by Weinland due to the presence of the slit in the body of the female where the male is sheltered). Human infections are caused mainly by the Schistosoma mansoni, Schistosoma haematobium, and Schistosoma japonicum, respectively in their specific regions [3].

The life cycle of the parasite begins with the presence of its eggs in a fresh water reservoir. There they hatch and release the miracidium, the swimming larval form of the worm. The miracidium infects the intermediate host of the cycle: snails (Biomphalaria species to S. mansoni, Bulinus species to S. haematobium, and Oncomelania species to S. japonicum). Over 30 days they suffer morphologic modifications and are released again in the water in a caudate form named cercariae. The cercariae penetrate the skin of the definitive host, a human or other mammal, shed their tail becoming schistosomula, and reach the venous circulation en route to the lungs. In the pulmonary capillaries they perforate the alveolar-capillary barrier and go up the bronchial tree until the pharynx where they are swallowed. They reach the gut and migrate to the portal venous system where males and females mature and unite. Pairs of worms then migrate to the superior mesenteric veins (S. mansoni), the inferior mesenteric and superior hemorrhoidal veins (S. japonicum), or the vesical plexus (S. haematobium). Egg production begins 6 weeks after the primal infection and persists throughout the life of the worm, usually 3–5 years (there are, however, anecdotal reports of worms with 30 years of active life). The eggs then pass from the lumen of blood vessels into adjacent tissues, and many reach intestinal or bladder mucosa and are shed in the feces (S. mansoni and S. japonicum) or urine (S. haematobium). The life cycle is completed when the eggs reach a reservoir of fresh water reservoir [10].

About one third of the eggs produced by S. mansoni and S. japonicum do not follow the direction of the intestinal lumen and are deposited instead in the small veins of the liver as a natural consequence of the portal flow. During the late schistosomal infection, the immunologic response is mainly a CD4 lymphocyte T helper 2 one, with the mediation of IL-4 and IL-13, among other chemokines. The shift of response from T helper 1 to T helper 2 from the host is responsible for the formation of the granulomatous activity. The eggs therefore induce a presinusoidal granulomatous inflammatory response and periportal fibrosis with subsequent portal hypertension. In the presence of this condition, portacaval shunts open; in addition to the generation of pulmonary blood overflow, it enables the eggs to be carried to the lung capillaries where they lodge [11]. Most of the lesions associated with chronic schistosomiasis are not related to the worms, but to the released eggs and the secondary granulomatous inflammatory T helper 2 response. Some genetic factors of the definitive host are known to be related to the magnitude of this granulomatous response, particularly in the liver. Whether these factors are also co-related with the development of PH in the schistosomotic population remains to be studied.

Since the disease is mainly located in presinusoidal space, sparing the hepatocytes, liver failure is usually not a feature of schistosomiasis, even in the presence of advanced hepatosplenic disease and portal hypertension.

The Development of Pulmonary Hypertension in Schistosomiasis

In 1938 Shaw and Gareeb [12] published a case series of Sch-PH. Based on the presence of the eggs in the pulmonary vessels, they believed that the eggs had a mechanical effect and induced PH by physical vascular obstruction, basically due to the embolic mechanism, inducing secondary right ventricular insufficiency, and suggested the first proposed mechanism of the genesis of PH in schistosomiasis.

Ever since the 1960s, this hypothesis was contested. Pathologic studies of this period indeed identified the presence of eggs in the vessels of Sch-PH patients. Nevertheless, it was found in both frequency and magnitude to be clearly insufficient to generate PH merely by physical vascular
obstruction. Some authors then hypothesized that the presence or maybe just the passage of the eggs or the worm during its life cycle induces nongranulomatous inflammatory endothelitis in the pulmonary circulation of genetically susceptible patients, and the abnormal healing process would be responsible by the PH genesis. Chaves [13, 14], among others, did not identify marked pathologic differences in the plexiform lesions of Sch-PAH and primary PH [nowadays idiopathic PAH (IPAH)] patients. Besides, the plexiform lesions of Sch-PAH did not present any relation to the angiomatoid lesions characteristically related to the schistosoma egg when these were found [13–14]. These data were re-evaluated and confirmed in a case series that also supported the existence of a spectrum of vascular lesions not related to the presence of eggs or granuloma [15] (fig. 1).

Recently, an experimental study in mice identified a direct relation between the quantity of schistosoma eggs in the pulmonary circulation and the induced granulomatous response with the degree of right ventricle remodeling. It is possible then to speculate that the inflammatory response may be proportional to the quantity of antigen released in the lung tissue, reinforcing the possibility of this so-called ‘inflammatory’ mechanism of disease. Different cytokines have been implicated with the immunological processes that modulate chronic host response to schistosoma infection (mainly in the setting of hepatosplenic disease), as IL-13, interferon-γ, TNF, and IL-5. Nevertheless, their specific role in each phase of human schistosomiasis is still to be determined [16].

Nevertheless, it is quite evident that not just the exposure to the schistosoma egg is enough to induce PH in schistosomotic patients. The low relative prevalence of PAH in schistosomiasis (4.6%) is evidence that other factors may intervene in the PH genesis [7], otherwise all schistosomotic patients would develop PH. In light of this information, some authors have hypothesized that Sch-PAH may not be related to the egg presence at all and may be just another form of portopulmonary hypertension, where, in patients with portal hypertension, the opening of portacaval shunts would generate blood overflow in the pulmonary circulation and subsequently endothelial dysfunction and PH [17]. In fact, Sch-PAH shares with portopulmonary hypertension many clinical features (e.g. the better hemodynamic profile at diagnosis and the lack of acute response to vaso-dilator challenge) [18]. Again, however, the prevalence of Sch-PAH leaves some doubt about this theory. While just 1–2% of patients with portal hypertension develop PH [19], more than the double of this prevalence is found in Sch-PAH, meaning at least that the schistosomotic patient is more susceptible to pulmonary blood overflow than the ordinary patient with portal hypertension. This is possibly due to the presence or passage of the egg in the lung vessel and may be secondary to the inflammatory response induced by it. Today it is believed that, besides an individual predisposition, Sch-PAH may be related to multiple hit mechanisms, including mechanical impaction of S. mansoni eggs within the pulmonary vessels, the consequent inflammatory process in the lung vasculature, and the higher blood flow that...
occurs in portal hypertension because of arteriovenous shunts.

The classification of schistosomiasis in the setting of PAH follows the timeline of it becoming better understood. In 1988, the Evian classification of PH put schistosomiasis in the inflammatory group along with sarcoidosis, which could have had incorrect implications in terms of treatment [20]. The revised classification, from the international symposium held in Venice in 2003 [21], relocated schistosomiasis in the nonthrombotic embolic group, emphasizing the mechanical effect of egg obstruction in the lung vasculature. In 2008 at the last international symposium held in Dana Point, schistosomiasis was reclassified as a form of PAH (Group I), reflecting recent findings regarding pathology and hemodynamic presentation [9].

Clinical Features of Pulmonary Hypertension Associated with Schistosomiasis

Clinical presentation of Sch-PH is very similar to that of IPAH [7]. The symptoms of progressive dyspnea, chest pain, dry cough, lower-extremity edema, and eventually syncope may be present, which worsens progressively over years at a rate slower than the progression of IPAH. Recent data show other similarities among these two entities concerning clinical aspects, such as mean age at diagnosis (roughly the third to fifth decade of life), functional class at diagnosis, and baseline 6-min walk time [18].

It is known that the initial contact with the parasite might happen many years before the onset of PH symptoms and still be schistosomiasis that is responsible for the disease since it is the consequence of the egg position which is responsible for the genesis of PH and not necessarily active schistosomiasis. In other words, a patient exposed to the worm in childhood, even if adequately treated ensuring the elimination of the parasite, may develop PH in his 40s or 50s, depending on the time of the exposure and the individual predisposition [13]. Therefore, the epidemiologic information about schistosomiasis always needs to be researched, even in nonendemic areas, since the patient may originally be from a high prevalence region of the disease.

Remarkably, most Sch-PH patients do not present with severe symptoms of portal hypertension and the diagnosis of schistosomiasis is usually given much later than the diagnosis of PH. Considering these data, it is possible to imagine that schistosomotic patients that evolve to PH may be the ones in whom the portacaval shunts are more effective, sparing somehow the portal circulation after the beginning of the process.

The radiological features somehow reinforce this hypothesis since they suggest an insidious process with remarkable vascular dilatations [22]. The main pulmonary artery enlargement is more pronounced when compared with IPAH, even considering the severity of the hemodynamic profile, and are similar to the ones found in congenital heart disease-associated PH, suggesting a slower rate of progression and greater compliance of the pulmonary arteries (fig. 2).

Diagnostic Strategy

The diagnosis of schistosomiasis is based mainly on environmental exposure to the parasite and identification of the parasite eggs in stool examination or rectal biopsy [10]. Abdominal ultrasonographic findings such as enlargement of the left lobe of the liver or periportal fibrosis may suggest schistosomiasis and have a high positive predictive value in prevalent areas [23]. These hepatosplenic abnormalities may support the association of schistosomiasis with PAH; however, schistosomiasis may also cause PAH in the absence of portal abnormalities. Serologies, by means of ELISA technique, may identify previous contact with multiple forms of Schistosoma, but utility is mainly in patients from nonendemic areas since the massive population exposure lowers the value of serologies as a disease marker [24].
The cardiovascular investigation of Sch-PH follows the same algorithm suggested for other etiologies of PH. After clinical suspicion, an echocardiogram is performed; when signs of PH are present, right heart catheterization is mandatory to confirm elevated pulmonary artery pressure and determine the main vascular territory implicated (pre- or postcapillary) [25]. A recent study comparing consecutive newly diagnosed patients with schistosomiasis-related PAH and IPAH from the same period of time showed that schistosomiasis patients displayed a more preserved hemodynamic profile at diagnosis. Furthermore, none of the schistosomiasis patients displayed acute vasodilation in response to nitric oxide challenge as compared with an approximate 15% response in the idiopathic [18].

The prognosis of Sch-PH also seems to be better than IPAH. Recent data demonstrated that independently of hemodynamic severity at baseline, Sch-PH patients had a better 3-year survival than what would be expected for patients with IPAH, suggesting a more benign course of the disease (86 vs. 52%, respectively) [18]. These findings are similar to what is believed for portopulmonary hypertension, as recently demonstrated by Le Pavec et al. [26], mainly if the subgroup of patients without liver cirrhosis is considered, which is another similarity between these two conditions.

**Therapy of Pulmonary Hypertension Associated with Schistosomiasis**

Conventional therapy for PAH such as diuretics and oxygen should be implemented as needed to all patients with Sch-PH. Particularities in the conventional therapy for PAH to this population of patients includes caution in the implementation of anticoagulation since there is a risk of life-threatening bleeding due to the presence of esophageal varices. The use of high-dosage calcium channel blockers is not advised because of the presence of portal hypertension in virtually all cases, and absence of response to the vasodilator test.

The response of schistosomiasis-associated PAH to specific PH therapy requires further study. Preliminary reports noted improvement in right ventricular function with sildenafil (assessed by MRI) [27]. There is a theoretical benefit in the use of endothelin receptor antagonists or prostanoids, but hard data is lacking. Unpublished data from our group demonstrated a statistically significant improvement of baseline hemodynamics and clinical parameters (6-min walk test and functional class) with specific PH treatment available (sildenafil and bosentan), but further studies addressing endpoints such as mortality or time to clinical worsening with specific PH therapy are still needed.

The effect of antiparasitic treatment in the course of Sch-PH is questionable. In theory, it would be interesting to decrease the rate of egg position and, consequently, the time and quantity of antigen exposure, decreasing the secondary inflammatory response. Nevertheless, a great number of Sch-PH patients do not carry the viable worm at the time of diagnosis. In the hepatosplenic disease, response to antiparasitic treatment varies greatly, ranging from no effect to resolution of periportal fibrosis [28]. Antiparasitic treatment is not believed to have a significant effect on the pulmonary circulation, but at least one case report cited significant improvement in hemodynamics after treatment [29]. However, as the treatment of the parasite requires one-day treatment with praziquantel, a drug with few side effects, it is reasonable to treat all diagnosed patients even in the absence of viable worms or eggs.

**Conclusion**

Schistosomiasis is one of the most prevalent chronic infectious diseases in the world. One of its most severe complications is PH, which may occur in up to 5% of patients with hepatosplenic schistosomiasis. The prevalence of schistosomiasis is so overwhelming that Sch-PH may be the most prevalent cause of PH around the world. Nevertheless, despite its epidemiologic importance, much still remains to be understood about this disease. Multiple pathways have been described as potential mechanisms of diseases of Sch-PH, such as egg embolism in a physical manner, egg-triggered inflammatory disease, or pulmonary blood overflow due to the opening of portacaval shunts in a similar way to portopulmonary hypertension; it is quite possible that each one of these has a role.

The clinical features of Sch-PH are very similar to the ones of IPAH, but less severe and with a longer evolution. The natural history of the disease was described, with a 3-year rate of survival of 86%. Nevertheless, the experience in providing health care to these patients shows that Sch-PH patients may take longer to deteriorate, but when they do they follow the same path downstream, such as IPAH.

The response to specific PH treatment still needs to be addressed, but small studies suggest a significant benefit with the use endothelin antagonist receptors and inhibitors of phosphodiesterase 5, concerning clinical and hemodynamic parameters. To date, there is no data available on mortality and specific PH treatment in Sch-PH.
References


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