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INFLUENCE OF THE (-G1082A) *IL-10* POLYMORPHISM IN SCHISTOSOMOTIC PATIENTS ON THE FOLLOW-UP OF SPLEEN, PORTAL VEIN AND SPLENIC DIAMETERS 2 YEARS AFTER SPECIFIC TREATMENT

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INTRODUCTION

MS is a neglected tropical disease with a major impact on public health, affecting around 1.5 million Brazilians. Brazil is considered the country in Latin America with the largest transmission focus, with a high prevalence in the Northeast region, especially the state of Pernambuco, where the frequency of the disease among the inhabitants of the Zona da Mata micro-region varies between 10% and 50% (Calasans *et al.*, 2018; Melo *et al.*, 2018).

The lesion resulting from the infection is predominantly caused by the host's immune response to the *Schistosoma mansoni* parasite eggs deposited in the liver, triggering chronic granulomatous inflammation, with consequent periportal fibrosis (PPF) and obstruction of the blood flow of the intrahepatic branches of the portal vein (PV). The deposition of *S mansoni* eggs also promotes immunological stimulation for hyperplasia of the reticulo-endothelial system of the spleen and consequently splenomegaly (Pordeus *et al.*, 2008; Magalhães *et al.*, 2004). These two processes can lead to the development of PH with the appearance of esophago-gastric varices and hypertensive gastropathy, important risk factors for bleeding. The rupture of esophageal varices is the most damaging complication of this disease, occurring in around 12 to 15% of patients and is the most frequent cause of death among those with schistosomiasis, occurring in around 20% of cases (Andrade, 2009; Gunda *et al.*, 2020; Machado *et al.*, 2002).

It is also known that the larger the varicose caliber, the greater the occurrence of bleeding (Santos; Ortolan, 2020). In addition, while progressive obstruction of the intrahepatic portal branches occurs, as a compensatory mechanism, there is an increase in the flow of the hepatic arterial system, especially in the region of the peribiliary vascular plexus. The diameters of the PV, LV and SMV increase in MS portal hypertension and may

decrease after splenectomy. Some authors report an increase in the caliber of the PV, splenic vein (SV) and superior mesenteric vein in 73%, 68% and 42%, respectively, as well as the identification of venous collaterals (left gastric vein, short gastric veins and umbilical veins) in 36% to 78% of cases (Andrade, 2008, 2009).

The development of PFP depends on several factors, mainly immunogenetic, and can be influenced by environmental factors, including gender, age, parasite load, alcoholism, frequency and time of exposure, among others, which can interfere in the development and severity of PFP (Silva; Domingues, 2013). On the other hand, the specific treatment of schistosomiasis allows for partial or complete reversal of PFP, and immune mechanisms are probably involved in this process (Andrade, 2005; Guevara *et al.*, 2007).

Among the immunogenetic markers involved in the fibrogenesis process is IL-10, an important anti-inflammatory, anti-immune and anti-fibrotic cytokine that regulates the inflammatory response and the formation of liver fibrosis, although its role in the activation and inhibition of PPF in MS is still unclear.

The *IL-10* gene contains 5 exons located between bands 1q31 and 1q32 of chromosome 1, and several polymorphisms have been described in its promoter region (Turner *et al.*, 1997). IL-10 levels vary widely between individuals, possibly because of these polymorphisms (Silva *et al.*, 2014, 2016). Some studies have shown an association between advanced PPF and high levels of IL-10 production (De Jesus *et al.*, 2004; Dessein *et al.*, 2009 Rachfal *et al.*, 2003), while others have associated low levels of *IL-10* with severe PPF in schistosomiasis (Booth *et al.,* 2004, Arnauld *et al.*, 2008).

Therefore, the role of this cytokine in this process is still controversial and its impact on PH is still little explored. It has been reported that the *-G1082A IL-10* promoter polymorphism was associated with PFP in individuals with MS in the state of Pernambuco (Silva *et al*, 2014). Thus, the impact of this polymorphism on PFP and consequently on PH in individuals with MS needs to be better elucidated. In view of this, it is possible that genotypic variants of the *IL-10* gene may be involved in the molecular mechanisms involved in PFP and possibly in PH in schistosomal patients (Silva *et al.*, 2014).

This study investigated the association of the polymorphism in the promoter region (-G1082A) of the Interleukin 10 *(IL-10*) gene with signs of portal hypertension (PH) observed by ultrasound (spleen diameters and portal and splenic vein calibers) before and during the 2 consecutive years after specific treatment for Schistosomiasis mansoni (MS), in patients from endemic areas in the state of Pernambuco, Northeast Brazil.

METHOD

This is a retrospective cohort study of 124 MS patients undergoing specific treatment with Praziquantel for schistosomiasis. This study investigated the association of the polymorphism in the promoter region (-G1082A) of the Interleukin 10 *(IL-10*) gene with signs of portal hypertension (PH) observed by ultrasound before and during the 2 consecutive years after specific treatment for Schistosomiasis mansoni (MS). To this end, a 2-year cohort of MS patients in the state of Pernambuco was followed up in order to understand the host-parasite genetic interrelationship, as well as the molecular epidemiology aspects involved in this process.

All patients were treated with Praziquantel at the Gastroenterology Outpatient Clinic of the Hospital das Clínicas of the Federal University of Pernambuco (HC/UFPE), Recife, Brazil. All the patients in this study came from an endemic area for schistosomiasis in the state of Pernambuco, northeast Brazil. These patients were divided into 2 groups: Group 1-

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(exposed): 71 patients with the polymorphic (-1082) GA or AA *IL-10* genotypes and Group 2- (unexposed): 53 patients with the (-1082) GG *IL-10* genotype.

INCLUSION CRITERIA

Patients over the age of 18 who underwent abdominal ultrasound (US) with confirmation of PFP, following the Niamey protocols (Ricther et al., 2001), before treatment for schistosomiasis and during the 2 years after treatment, were included.

EXCLUSION CRITERIA

Patients with a moderate pattern of PPF (Pattern D) were excluded. Those with other hepatopathies, such as liver cirrhosis, steatosis, hepatitis B or C and alcoholic disease that were ruled out by clinical history, abdominal US and specific laboratory tests (HBsAg, anti HBc, anti HBs and anti HCV); patients who had undergone blood transfusion in less than three months; other clinical forms of schistosomiasis already diagnosed, such as pulmonary vascular disorders, pseudo neoplastic forms, schistosomal nephropathy and medullary form were also excluded.

The outcomes of interest were objective ultrasound features (diameter of the spleen, portal vein and splenic vein) relating to the periods before specific treatment for MS and during the 2 consecutive years after this treatment for this 2-year cohort, which guarantees their comparability, in the context of the study hypothesis, as factors associated with the *(-G1082A) IL-10* polymorphism. And the main exposure of interest was the *(-G1082A) IL-10* polymorphism. Information on these genotypes was obtained in 2012 and 2013.

Information on these clinical variables was obtained from medical records using a specific form, after the patient had declared informed consent in the previous study (Silva, 2014).

DATA COLLECTION

The steps related to the diagnosis of the clinical forms of Schistosomiasis, biological samples, processing of biological material, method of molecular biology and genotypic categorization have already been done in the period 2012-2013, in a previous study (Silva, 2014).

The *IL-10* polymorphism *(-G1082A)* was determined by Allele-Specific Polymerase Chain Reaction at the Molecular Biology Laboratory of the Pediatric Oncohematology Center (CEONHPE-UPE) of the University of Pernambuco (UPE).

For this study, the association of the (-G1082A) *IL-10* polymorphism with ultrasonographic aspects of signs of PH was analyzed by analyzing the epidemiological and immunogenetic database of the "Clinical and Experimental Schistosomiasis" research group from August 2022 to August 2023. The dependent variables were analyzed: measurements of the diameters of the portal vein, splenic vein and spleen size, as well as the independent immunogenetic variables, which were the genotypes referring to the *IL-10* promoter region (-G1082A).

ULTRASOUND EVALUATION

The diagnosis of the clinical form of the disease was determined through the patient's clinical history and physical examination, as well as ultrasound evaluation of the upper abdomen by a single operator in the Gastroenterology Department of HC/UFPE, using a Siemens Acuson X150 ® device with a 3.5 mHz convex transducer, in order to confirm the diagnosis and exclude other liver diseases. The parameters used to define the PPF pattern were based on the Niamey classification (Richter *et al*., 2001): A- absence of fibrosis; B- doubtful fibrosis; C- mild; D - moderate; E - advanced; and F - very advanced. Meanwhile, the parameters adopted as normal and abnormal for measurements of the diameters of the

portal vein, splenic vein and spleen size (longitudinal axis) in this study were as follows: portal vein - normal ≤ 12 mm; splenic vein - normal ≤ 9 mm; longitudinal spleen size - normal ≤ 13 cm (Richter *et al.,* 2001).

DATA PROCESSING AND ANALYSIS

The follow-up period was considered from the moment the specific treatment was recorded for the first time until the 2 consecutive years of this. Crude Relative Risk (RR) and 95% confidence interval (95% CI) were used through bivariate analysis to verify the association between (-G1082A*) IL-10* genotype frequencies and sonographic factors among the exposure groups, considering the (-G1082A*) IL-10* polymorphism as the independent variable and the selected sonographic variables as dependent. The association was considered significant when $p < 0.05$. Epi-Info software version 7.02 (CDC, Atlanta, GA, USA) was used for these analyses

ETHICAL CONSIDERATIONS

This study was authorized by the Research Ethics Committee of the Health Sciences Center, UFPE, under protocol 113.199 and CAAE 03161512.6.0000.5208.

RESULTS

The average age of the sample was 57 years (± 13 years). There was no difference in gender distribution between the exposure groups (p= 0.349).

Table 1 shows that there was no association between the *(-G1082A) IL-10* polymorphism and spleen size before treatment for schistosomiasis (RR = 0.83; CI = [0.363-1.909]; p-value = 0.953). There was also no association between the *(-G1082A) IL-10* polymorphism and spleen measurement 2 years after specific treatment (RR = 0.62; CI = [0.306-1.292]; p-value = 0.491). (Table 1).

There was also no association between the (-G1082A*) IL-10* polymorphism and PV caliber before treatment for schistosomiasis (RR = 1.09; CI = [0.747-1.591]; p-value = 0.858) or in 2 consecutive years after specific treatment (RR = 0.97; CI = [0.720-1.065]; p-value = 0.457). (Table 2).

Table 3 shows that there was no statistically significant association between the *(-G1082A) IL-10* polymorphism and LV diameter before specific treatment for schistosomiasis (RR = 0.98; CI = [0.66-1.46]; p-value = 1.00). There was no statistically significant association between the *(-G1082A) IL-10* polymorphism and LV diameter 2 years after specific treatment for schistosomiasis (RR = 1.19; CI = [0.84-1.69]; p-value = 0.41). (Table 3)

DISCUSSION

In this study, no evidence was found of an association between the *IL-10* genetic polymorphism *(-G1082A)* and ultrasound features related to PH (longitudinal spleen size, portal vein size and splenic vein size) for the periods before specific treatment for MS and during the 2 consecutive years after this treatment.

Silva *et al* (2014) evaluated 203 patients infected with *S. mansoni* in Pernambuco and found that the *(-1082) AA and GA IL-10* genotypes were predictive factors for advanced standard PFP, unlike the *(-1082) GG IL-10* genotype. PPF is one of the morbidity indicators of *S. mansoni* infection, which can lead to PH and the formation of esophagogastric varices which, when ruptured, cause Upper Digestive Hemorrhage (UDH). It is possible that these genotypic variants of the *IL-10* gene may be involved in the molecular mechanisms of PFP and possibly associated with signs of PH in schistosomal patients.

Spleen size before treatment (N= 124)[a,b]							
	Normal		Abnormal				
	N	%	N	%	RR	95%CI	P-value
IL- 10* polymorphism *(-G1082A)*							
GA / AA	23	85,2	46	88,5	0,83	[0,363-1,909]	0,953
GG	4	14,8	6	11,5			
Total	27	100	52	100			
Spleen size 2 years after treatment (N=124) [c,d]							
	Normal		**Abnormal**				
	N	%	N	%	RR	95%CI	P-value
IL- 10* polymorphism*(-G1082A)							
GA / AA	23	85,2	41	93,2	0,62	[0,306-1,292]	0,491
GG	4	14,8	3	6,8			
Total	27	100	44	100			

Table 1: Analysis of the association between the *(-G1082A) IL-10* polymorphism and the longitudinal size of the spleen of 124 patients with Schistosomiasis mansoni before treatment with Praziquantel and 2 consecutive years, Pernambuco, 2022.

*2 participants did not have DNA amplified for the -1082 region (IL-10). a: 1 participant did not have information on spleen size in medical records. b: 42 participants were splenectomized. ****2** participants did not amplify DNA for the -1082 (IL-10) region. c: 1 participant did not have information on spleen size in medical records. d: 50 participants were splenectomized

Portal vein caliber before treatment (N=124) [a]							
	Normal		Abnormal				
	N	%	N	%	RR	95%CI	P-value
IL- 10* polymorphism *(-G1082A)*							
GA / AA	72	87,8	27	84,4	1,09	[0,747-1,591]	0,858
GG	10	12,2	5	15,6			
Total	82	100	32	100			
Portal vein caliber 2 years after treatment[b]							
	Normal		**Abnormal**				
	N	%	N	%	RR	95%CI	P-value
IL- 10* polymorphism *(-G1082A)							
GA / AA	74	82,2	21	91,3	0,87	[0,720-1,065]	0,457
GG	16	17,8	2	8,7			
Total	90	100	23	100			

Table 2: Analysis of association between portal vein caliber before specific treatment for schistosomiasis mansoni and 2 consecutive years and the *(-G1082A) IL10* polymorphism, Pernambuco, 2022.

*2 participants did not amplify DNA for region *-1082 (IL-10)*. a: 8 participants did not provide information on portal vein diameter in medical records. ****2** participants did not amplify DNA for region *-1082 (IL-10*). b: 9 participants did not have information on portal vein diameter in medical records

Splenic vein diameter before treatment (N=124)[a,b]							
	Normal		Abnormal				
	N	%	N	%	RR	95%CI	P-value
IL- 10* polymorphism *(-G1082A)							
GA / AA	26	60,5	19	61,3	0,98	[0,66-1,46]	1,00
GG	17	39,5	12	38,7			
Total	43	100	31	100			
Splenic vein diameter 2 years after treatment[c,d]							
	Normal		**Abnormal**				
	N	%	N	%	RR	95%CI	P-value
IL- 10* polymorphism *(-G1082A)							
GA / AA	32	65,3	12	52,2	1,19	[0,84-1,69]	0,41
GG	17	34,7	11	47,8			
Total	49	100	23	100			

Table 3: Analysis of association between splenic vein diameter before specific treatment for schistosomiasis mansoni and 2 consecutive years and the *(-G1082A) IL-10* polymorphism, Pernambuco, 2022.

a: 7 participants did not have information on the diameter of the splenic vein in their medical records. b: 43 participants were splenectomized. c: 3 participants had no information on splenic vein diameter in medical records. d: 49 participants were splenectomized.

On the other hand, Silva *et al* (2016) analyzed 119 individuals also infected with *S. Mansoni* in the state of Pernambuco and found that there was no significant association between the polymorphism of the *(-G1082A) IL-10* region and the regression of PFP, possibly due to ethnic variations in this population

The later the diagnosis of the patient with the HE form and advanced PPF, the greater the chance of esophageal varices. However, not all cases with PPF have esophageal varices and esophageal varices will not always rupture and bleed, especially in Brazil, where the frequency of ADH is lower than in Africa (Gunda *et al.,* 2020)

In a study of 123 individuals infected with *S. Mansoni* in the state of Pernambuco, it was observed that serum levels of IL-10 and polymorphism in the *IL-10* promoter region (-C819T) were also not associated with upper gastrointestinal bleeding (Constantino *et al.,* 2022).

There are reports that advanced PFP is related to low IL-10 production in schistosomotic patients (Booth *et al.,* 2004). Therefore, high IL-10 production would protect against fibrosis due to its anti-inflammatory effects (Arnaud *et al.,* 2008). However, there is controversy about the role of IL-10 in the development of PFP (Rachfal *et al.,* 2003; Dessein *et al.,* 2009).

Brandt *et al (*2010) evaluated 88 patients divided into three groups (Group I - 25 patients with the hepatosplenic form of schistosomiasis; Group II - 30 patients with schistosomiasis who had undergone splenectomy and ligation of the left gastric vein; Group III - 33 patients who did not have the hepatosplenic form or any other pathology that compromised the functioning of the hepatic system. They observed that IL-10 levels were not associated with PFP in these individuals.

In another study carried out in Bahia, Jesus *et al* (2004) investigated the relationship between type 2 cytokines and liver fibrosis and found evidence of an association between IL-10 and type III liver fibrosis.

Another complication associated with portal hypertension in MS is enlargement of the spleen, which is a consequence of alterations determined by different factors such as the constant elevation of venous pressure on this structure and the immune response to infection stimuli (Ferraz *et al.,* 2001). Splenomegaly in schistosomiasis seems to depend more on the hemodynamic component than secondary to immune alterations, and perhaps this fact explains the lack of association between genetic polymorphism and manifestations of portal hypertension in this sample. This was a retrospective study. There was no control over the patients who remained in or left the endemic area, which may also have influenced the results.

On the other hand, considering the limited sample size in this study, as well as possible ethnic variations in this population, further studies with larger samples and in other populations are recommended in order to better analyze and investigate the impact of the *(-G1082A) IL-10* polymorphism in altering portal hypertension in schistosomal patients.

In short, in this study, there was no association between the *(-G1081A) IL-10* polymorphism and spleen, PV and LV diameter, either before treatment for MS or at follow-up of up to 2 years

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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