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Experimental schistosomiasis in the Common Marmoset *Callithrix jacchus*

Esquistossomose experimental no Sagüi *Callithrix jacchus*

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ABSTRACT

In order to evaluate Callithrix jacchus *as an animal model for mansoni schistosomiasis, a group of 10 male animals were once percutaneously exposed to 250 cercariae of the* Schistosoma mansoni *SLM (São Lourenço da Mata) strain. Animals were periodically bled for measuring serum level of enzymes and proteins and for blood cell counting. When comparing pre-infection to post-infection values, a significant increase was found for alkaline phosphatase at 15 to 120 days p.i., differential counts of eosinophil at 45 and 60 days, and total protein and global eosinophil counts at 120 days. No* Schistosoma mansoni *eggs were found in stools. Adult worms of small size were recovered from five animals. At day 120, the number of* Schistosoma mansoni *eggs/g of tissue was 0-289.7 (liver), 0-30.1 (large intestine) and 0-171.4 (small intestine). These findings lead us to classify* Callithrix jacchus *as a non-permissive host to the SLM strain of* Schistosoma mansoni.

Key-words: Callithrix jacchus. *Schistosomiasis.*

RESUMO

Com o objetivo de avaliar o Callithrix jacchus *(sagüi) como modelo experimental para a esquistossomose, um grupo de 10 animais, machos, adultos jovens, foram expostos a 250 cercárias da cepa SLM (São Lourenço da Mata) do* Schistosoma mansoni*, pela via percutânea. A intervalos de 15 dias até 120 dias apos infecção foram dosados os níveis de proteínas totais e enzimas séricas, além de realizados exames parasitológico e hematológico. Aumento significativo foi observado para: fosfatase alcalina a partir do 150 dia; contagem global de eosinófilos aos 120 dias, e diferencial de eosinófilos aos 45 e 60 dias p.i. Nao se observou ovos de* Schistosoma *nas fezes. Á perfusão cinco animais apresentaram vermes adultos. Todos os vermes encontrados eram diminutos. O número de ovos foi 0-289,7 ovos/g de tecido no fígado, 0-30,1 no intestino grosso, 0-171,4 no intestino delgado. Esta observaçoes levam-nos a concluir que o* Callithrix jacchus *seja não-permissivo ao* Schistosoma.

Palavras-chaves: Callithrix jacchus. *Esquistossomose.*

It is estimated that more than 200 million people are infected in 76 different countries worldwide and about 600 million people are at risk of becoming infected with the trematode *S. mansoni*[6 27 29 31]. This parasite inhabits the blood veins of mammals and causes a disease called schistosomiasis.

In Brazil, mansoni schistosomiasis is present as an endemic disease in some states of the Northeast and Southeast regions. There are approximately 10 million Brazilians infected with the disease[1]. In Pernambuco, mansoni schistosomiasis occurs in both the coast and in the area of

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abundant vegetation called *Zona da Mata*. For instance, in 4 villages of São Lourenço da Mata, a municipality 25km northwest from Recife, approximately 99.6% of the inhabitants were infected with at least one species of intestinal parasites. Prevalence for *S. mansoni* was 82.1% in this area[17 18 44].

Infections due to *Schistosoma* have been studied in many animals including mice, rats, guinea pigs, rabbits, cows and non-human primates. Nevertheless, doubts remain about whether or not a specific animal is the correct representation of the disease in humans. Many mammals have been described as carrying natural infection with *S. mansoni*. For example, cows have been described as having natural infection or as being susceptible to *S. mansoni* infection[27 12]. *Rodentia* is the Order with the largest number of species found having natural infections. *Nectomys squamipes* has been found naturally infected with *S. mansoni* in many states in Brazil[3 10]. In rodents infected with 500 *S. mansoni* cercariae from any strain and by either percutaneous or subcutaneous routes, approximately 10% of the cercariae can be recovered as adult worms[25]. On another study, *Nectomys rattus* presented an infection rate of 71%[38].

Although monkeys are phylogenetically more closely related to humans, their use as laboratory animals is restricted to cases in which animals traditionally used in laboratory research can not be used with satisfactory results[2]. In schistosomiasis, monkeys show some advantages compared to the common laboratory animals since as they maintain a semi-erect position, their portal-mesenteric circulation dynamics may be closer to that of humans. Also they have a higher hepatic tissue volume, enabling a better comparison to lesion in humans[4]. In addition, they live longer enabling their study over a period of years, which is important when one considers that humans usually carry their infection for many years.

A non-permissive host to *S. mansoni* is defined as an animal in which the worm development is incomplete and/or oviposition is not sustained for a long period. As in the case of the *Rhesus* monkeys, which pass *S. mansoni* eggs in their feces for only about a year. Rats, rabbits and guinea pigs are all considered examples of non-permissive hosts to *S. mansoni*. On the other hand, in permissive animals, oviposition is maintained for long periods. This requires that male and female adult worms mature and migrate together, to the lower mesenteric veins where oviposition begins. Humans, some species of monkeys, hamsters, and mice are all classified as permissive hosts. Parameters of infection that can be used to identify permissive or non-permissive hosts include number, size, morphology, and localization of adult worms, level and duration of oviposition, maturation of eggs, and level of pathology observed in the host[11 15].

Many primate species had been tested and are believed to be susceptible to *S. mansoni* infection. However, the level of permissiveness to *Schistosoma* varies considerably between different species of monkeys. According to Coelho *et al*[4], Leiper was the fist worker to infect *Mangaby sooty* monkeys with *Schistosoma mansoni* in his classical works in which he tried to show mammals' susceptibility to this parasite. Experiments on *Rhesus* monkeys carrying an initial *Schistosoma mansoni* infection showed that after a challenger infection, those animals were able to eliminate the new infective cercariae without being able to destroy the adult worms resulting from the previous infection. This brought up for the first time the concept of *concomitant immunity* in schistosomiasis[41 43]. *Cebus* monkey when infected orally and transcutaneously with the LE strain of Schistosoma mansoni, 30-50% of the cercariae are recovered as adult worms. However, there is no evidence of concomitant immunity[7 22]. When infected subcutaneously, tamarin monkeys met the criteria of permissiveness to *S. mansoni*: correct anatomical distribution of adult worms and oviposition for long periods of time[15]. Baboons have been found to be a permissive host for *S. mansoni* and a good animal model for schistosomiasis. Besides experimentally infected with *S. mansoni*, baboons are also naturally infected with this parasite. Muller-Graf *et al*[30], studying five troops of olive baboons (*Papio cynocephalus anubis*) in Gombe Stream National Park in Tanzania, found three troops naturally infected with *S. mansoni*. These authors affirm that the epidemiology of *S. mansoni* in baboons may display characteristics that are very close to human infection. In addition, baboons can both maintain and transmit *S. mansoni* parasite in the wild[34]. In baboons, 78% of cercariae can be recovered as adult worms. This percentage is usually 25 to 40% in mice and 15 to 20% in rats[47]. However there are some disadvantages of using baboons as a model for schistosomiasis, such as the high cost of buying and maintaining baboons in the laboratory, and the need for qualified personnel to care for the animal's health.

Callithrix jacchus, also known as common marmoset, is a small neotropical primate. It belongs to the *Callithrichidae* family and inhabits the Brazilian northeast forests[26]. *Callithrix* lives in small groups where the majority of the members are related. In the group there is one reproductive female and many other non-reproductive females. Its diet usually comprises of fruit, nectar, blooms, insects, and gum from some forest trees. This marmoset usually gives birth to two or more offspring at once. Parental care, which includes carrying, caring, and sharing food with the newborn, is performed by all adults and adolescents in the group[35].

Marmosets have many advantages as a laboratory animal. Their small size and high level of reproduction in captivity are very important factors. They are also easy to handle, require small amounts of food and show a high level of adaptability to new environments. *Callithrix* are currently used in experiments involving toxicity, viral, parasitological and bacterial diseases, and immunological research, contributing to the conclusion of important studies[2 35].

The objective of the present work was to evaluate the marmoset *C. jacchus* as a possible animal model for mansoni schistosomiasis.

MATERIAL AND METHODS

Experimental infection and blood collection. A group of twelve adult male *Callithrix jacchus* (weighing approximately 300g) were used in the experiments. Ten constituted the experimental group and two served as uninfected controls.

Callithrix jacchus were anesthetized and then exposed percutaneously to a pool of 250 cercariae of *S. mansoni*, SLM strain, placed in their inguinal area for 30 minutes under artificial light[15]. This *S. mansoni* strain had been maintained in *Biomphalaria glabrata*/ *Swiss* mice system. As a control for the cercariae infectivity, *Swiss* mice were also infected with the same pool of cercariae used in the marmoset infection.

After infection, at intervals of two weeks, animals had 1ml of blood drawn from their Femoral artery after anesthesia with ketamine. Serum was used for biochemical tests, and a small aliquot of blood treated with EDTA was used in the hematological analysis.

Animals had their weight measured and stools collected at the same time periods and in addition any signs of clinical symptoms were noted.

Biochemical tests & hematological counts. Biochemical manual assays were performed using commercial kits *Labtest*. In order to complete the entire battery of proposed tests with a small amount of blood, the volume of reagents used was proportionally divided by 5 (alanine amino-transferase, aspartate amino-transferase, alkaline phosphatase, total protein, and gamma-glutamyl transferase) or 2 (albumin).

Differential counts of blood cells were performed on a thick blood film stained with Giemsa (100 cells counted). At this time, it was possible to take note of any alteration in cell morphology and staining characteristics. Global counts were performed in a cell count chamber.

Parasitological analysis. Sedimentation[20] and formalin ether concentration[39] techniques were used to detect *S. mansoni* eggs and other forms of parasites in stool samples. When the amount of sample was not sufficient for performing both methods, preference was given to the concentration technique.

Animals were perfused at 120 days post infection. In the method used, portal hepatic and mesenteric system are perfused separately. Recovered worms were counted and sorted by sex under the stereoscopy. Liver, intestines, and spleen were weighted. Part of liver and intestines was used both for the hydroproline assays and for *S. mansoni* eggs identification after digestion with 5% potassium hydroxide (KOH). Tissue digestion using 5% KOH was done according to the technique described by Cheever *et al* [8] using 4 samples of 2g from liver and intestines (2 from small intestine and 2 from large intestine) for each animal.

From each animal, six samples of liver, of 0.5g each, were used for the hydroxyproline determination. After perfusion, tissue samples were frozen until processed according to techniques described by Cheever *et al*, Prockop *et al*, and Bergman et al[4 7 36].

In addition, spleen, kidneys, lungs, heart, and part of liver and intestines were kept in 10% formalin buffer for posterior histopathological analysis.

Statistical analysis. Paired Student's T test was used when comparing results for the same animal at different time points ($\alpha = 5\%$). Unpaired Student's T test was used to analyze the variations in global cell counts and organ weight values ($\alpha = 5\%$).

RESULTS

The mean biochemical values from day 0 to 120 days post infection (dpi) were: albumin 3.9-5.1g/dl, total proteins 6.7-7.6 g/dl, gamma glutamyl transferase 43.8-105.8 U/l, alkaline phosphatase 26.2-89.2 U/l, alanine amino-transferase 103-126.9 U/l and aspartate amino-transferase 5.8-20.2 U/l. When comparing values post infection (from 15 to 120 dpi) with the values pre infection (at 0 dpi), there was a statistically significantly increase in the serum levels of alkaline phosphatase from 15 dpi, and in the total protein levels at 120 dpi. However, the biochemical serum values of infected animals were within the normal limits for their species for most of the proteins measured, and considered as a whole, did not represent the characteristic changes observed in human schistosomiasis.

There was no sign of neutrophilia, but eosinophilia (26% at 120 days p.i.) was observed during the infection period, although other parasites that can increase eosinophil counts in blood were also detected in some of the animals studied such as *Strongyloides*. *Trypanosomatidae* were found on thick blood film samples of 3/10 animals and Filariidae worms were isolated from the lungs of 2/10 animals at perfusion.

Schistosoma mansoni eggs could not be found in the infected animal feces during all the observation time. However, five animals (#1, 2, 3, 4, and 8) presented *Strongyloides* larvae in their feces in the first 30 days of infection. After 105 dpi, three of the previous five animals (#2, 3, and 4) were positive again for *Strongyloides*.

After digestion with KOH the amount of *S. mansoni* eggs per gram of tissue present in liver and intestines of infected animals is shown in Table 1. In the liver samples of infected animals, *S. mansoni* eggs were found in 7/10 animals, *Eimeria sp* cysts were found in 6/10 animals, and both parasites were found in 3/10 animals. On the other hand, in the intestine samples, *S. mansoni* eggs were present in 5/10 animals, *Eimeria sp* in 6/10 animals, and both in 2/10

Table 1 - Number of eggs of S. mansoni *and cysts of* Eimeria sp *per g of tissue of* C. jacchus *infected with* S. mansoni *at 120 days post-infection.*

	Liver		Large intestine		Small intestine	
Animal	*S. mansoni*	*Eimeria sp*	*S. mansoni*	*Eimeria sp*	*S. mansoni*	*Eimeria sp*
1	249.3	0	30.1	0	27.8	0
2	5.5	0	0	0	0	0
3	0	88.6	0	5.5	0	0
4	289.7	0	16.2	0	171.4	0
5	109.8	1,495.8	0	30.8	0	254.8
6	3.8	2,508	0	22.2	0	6.3
7	0	114.7	0	70	0	0
8	30.9	951.7	18.4	5.5	0	0
9	308	0	13.6	0	40.4	258.5
10	0	49.8	0	0	2.0	0

animals. *S. mansoni* tissue egg counts varied from 0-289.7 in the liver, 0-171.4 in the small intestine, and 0-30.1 in the large intestine. Uninfected animals did not show any parasite form after KOH digestion.

Although *S. mansoni* eggs were found in tissue samples, the macroscopic changes due to their presence were not observed. A statistically significant difference ($p < 0.05$) was found in the weight of large intestine and liver of infected animals when compared to uninfected controls (Table 2).

Table 2 - Mean organ weight (± standard deviation) of controls and infected C. jacchus *at 120 days p.i.*

	Liver	Large intestine	Small intestine	Spleen
Control animals (n=2)	9.16± 0.33	5.81± 0.27	8.79±2.64	0.4±0.2
Infected animals (n=10)	13.04±1.87*	4.41±0.77*	7.37±0.65	0.57±0.13

$p < 0.05$

As shown in Table 3, at perfusion, the total number of adult worms recovered varied from 1 to 14 (0.4 to 5.6%). The male/female ratios were 10/1, 4/1, 0/0, 0/1, 1/6. Only one worm pair was found. Some immature forms of worms were observed and all worms were of small size and located mainly within the liver blood system and not in the mesenteric system.

Table 3 - Number of S. mansoni *adult worms and their localization in* C. jacchus *at 120 days post-infection.*

	2	4	7	6	9	Total
Portal- hepatic blood vessel system						
male	4	2	0	0	1	7
female	1	0	0	1	6	8
immature	0	1	5	0	0	6
pair	0	0	0	0	0	0
Subtotal	5 (50%)	3 (21%)	5 (100%)	1 (100%)	7 (100%)	21
Mesenteric blood vessel system						
male	5	6	0	0	0	11
female	0	2	0	0	0	2
immature	0	1	0	0	0	1
pair	0	1	0	0	0	2
Subtotal	5 (50%)	11 (79%)	0 (0%)	0 (0%)	0 (0%)	16
Total	10 (4%)	14 (5.6%)	5 (2%)	1 (0.4%)	7 (2.8%)	37

There was no significant increase in the amount of hydroxyproline due to *S. mansoni* infection. The mean amount of hydroxyproline per gram of tissue was 6.33 ±0.72mg in the uninfected animals (n = 2) and 6.41 ±1.65mg in the infected animals (n = 10). When comparing the value of hydroxyproline at 120 dpi with the value of hydroxyproline in the control animals, only in 4/10 animals a hydroxyproline gain of 0.77-3.55mg was observed. However, no *S. mansoni* egg was found in one of those animals, only *Eimeria sp*. The mean amount of hydroxyproline produced by egg laid in the liver was 260hg.

Infected animals did not present weight loss or any other clinical symptoms during the study.

Histopathologic examination was not one of the objectives of the present work. However, in our pilot study [42], ten *Callithrix jacchus* were percutaneously infected with 150 cercariae of the SLM strain of *Schistosoma mansoni*. Out of ten animals, 5 showed granuloma in their livers, 2 animals had granuloma in their intestines, and one animal had granuloma in a lung. *S. mansoni* eggs were found in the lungs of 3 animals, and in the liver of 7 animals. Out of 5 animals observed, there were no eggs in the intestines of any animal, adult worms were found in 4 of them, and no sign of fibrosis was found in any of the 5 animals. In another 5 animals, adult worms were found in samples of lung in one animal, in the liver of another, and in both liver and lungs of a third animal.

DISCUSSION

Hepatic function is usually well preserved in schistosomiasis. Patients have: 1) blood level of albumin bellow normal values; 2) levels of alkaline phosphatase and gamma glutamyl transferase above reference values, 3) levels of aspartate amino-transferase and alanine amino-transferase within the normal range or slightly elevated, 4) normal bilirubin; and 5) normal or slightly higher total protein amount in their sera[13 16 37]. In the present study, biochemical values of a set of enzymes and proteins that are related to liver function and that provide information to differentiate schistosomiasis from hepatic diseases due to other etiologies did not change characteristically.

Baboons show clinical symptoms characteristic of both acute and chronic stages of *S. mansoni* infection. Some of those symptoms were diarrhea, weakness, weight loss (acute stage) and histopathological changes (chronic stage)[14]. On the other hand, Cebus monkeys only presented symptomatology when experimentally infected with *S. mansoni*[4 7 22]. Unlike those other primates, *C. jacchus* showed no clinical symptoms during either acute or chronic stages of infection.

Leukocytosis was not present in our animal samples as has already been described in humans[32 37] and infected mice[23]. Eosinophilia, although present, cannot be attributed to *S. mansoni* alone, since other parasites that may also raise eosinophil counts in the blood were found in samples of some animals. *Callithrix* seems to bear parasite infections very well since no major clinical symptoms or biochemical changes were seen in those animals.

The fact that infected *C. jacchus* does not pass *S. mansoni* eggs in their feces is a characteristic different from that seen in human and other animals. In areas of high prevalence and moderate intensity of infection for schistosomiasis, the majority of infected people will pass a small number of eggs in their feces, while a small number of patients will pass a large number of eggs. Tanabe *et al*[44] reported that in São Lourenço da Mata, in Pernambuco State, Brazil, 61% of the infected population passed 1-100 egg/g of feces, while only 6% passed more than 401 eggs/g of feces. *Cebus* monkey, tamarin, and *Papio cynocephalus* all showed eggs in their feces at about 35 days pi[4 7 15 22]. In tamarins, this number was

higher in animals infected subcutaneously. Cows infected with 25,000 cercariae first showed eggs in their feces between 79 and 202 days pi[27]. The fact that no eggs were seen in feces of infected *C. jacchus* may be explained by an immunological factor characteristic of the specis. For example, Karanja *et al*[21] studying humans co-infected with HIV and schistosomiasis, observed that patients with a reduced number of CD4+ cells passed less eggs in their feces. Those authors report that some studies in humans, baboons, and mice, suggest that CD4+ cells are involved in the excretion of *S. mansoni* by infected hosts.

Although *S. mansoni* eggs were found in samples of intestines and liver, their number was very small. Considering that a *S. mansoni* female adult worm lays a large number of eggs per day, and that only a small part of them passes through the feces while the majority remains in the tissue. Handerson *et al*[19], for example, infecting inbred CB/J mice, found a range of 25,511-40,143 egg/liver depending on whether the animal developed *moderate splenomegaly syndrome* or *hypersplenomegaly syndrome*. In addition, in our study, macroscopic and physiologic changes due to the presence of *S. mansoni* eggs on the specified organs were not observed.

Schistosoma mansoni infection in human and other animals is usually followed by high levels of hydroxyproline, reflecting the level of hepatic fibrosis in those hosts. However, hydroxyproline gain due to *S. mansoni* infection was low and unspecific in our animals.

The morphology, small size and number (0.4% to 5.6% recovery), and mainly portal hepatic localization of *S. mansoni* adult worms recovered from *C. jacchus* do not reflect what has been seen so far in animals tested and considered permissive to *S. mansoni*. In *Papio anubis* and *Papio cynocephalus*, the percentage of cercariae recovered as adult worms is 78% and 42%, respectively[14]. Tamarins, if percutaneously exposed, show 2.6% of cercariae recovered as adult worms, but if subcutaneously exposed this value is 31.3%[15]. In mice, this value ranges from 25 to 40%, while in rats from 15 to 20%[47]. For *Nectomys squamipes* it has been observed as being 11.5%[25]. For cows, this value was 2.2%[27].

In baboons, maturation of cercariae often exceeds 90%. Female adult worms of *S. mansoni* start laying eggs around 5-6 weeks p.i. with a large number of eggs laid per worm pair per day. These eggs are found mostly in the intestines (80%) while around only 10% are found in the liver similar to a human infection. Infected animals present symptoms of the disease, and two clinical phases of the disease can be recognized. The first or acute phase starts at around 6-12 weeks p.i., and then there is a chronic phase after which some animals show granuloma, modulation of granuloma, and development of periportal fibrosis[28 34].

Lima *et al*[24], studying dyslipoproteinemia in *C. jacchus* (body weight 100-300g) infected percutaneously with 150-450 cercariae of *S. mansoni* (SLM strain), have reported that the parasite infection was confirmed at autopsy by histological examination of the liver. Nevertheless, no information was given on the number, size and localization of adult worms, number and viability of eggs, or any detail on the histological examination that was performed.

According to Rodrigues *et al*[40], *C. penicillata* (body weight 160-172g) infected by inoculation of 200 cercariae shows signs of granuloma around *S. mansoni* eggs and presence of adult worms on histopathological examination of the liver. However, the authors did not provide any information about the strain of *S. mansoni* used in the infection. In addition there is no information on: number or size of granulomas, egg counts, and morphology, localization and percentage of recovery of adult worms.

Sadun *et al*[41] also found signs of granuloma on four *Callithrix aurita* infected percutaneously with 50 (two animals) and 1000 (two other animals) cercariae of *S. mansoni* Puerto Rican strain. In this article, the authors investigated the percentage of adult worms recovered, localization and morphology of worms, the length of pre-patent period, number of eggs in the feces, number and localization of eggs in the tissue, egg viability, gross pathology and histopathology of organs such as lungs, liver, and intestines, and for the signs of other infections. They tried to classify the 10 species of monkeys into 3 groups according to their levels of permissiveness to *S. mansoni*. Although they saw some signs of granuloma in *Callithrix*, based on this and all other characteristics of this species they classify *Callithrix*, squirrel monkey, and the tree shrew monkey in the group they refer to as the *poorer hosts group*.

Similarly to *Callithrix jacchus* in our study, owl monkeys (*Aotus nancymai*) when infected with J.L. Venezuelan strain of *S. mansoni*, passed no eggs in their feces during a period of 16 weeks p.i. Although diarrhea and weight loss occurred, no adult worms were found by either perfusion or examination of fresh tissue. Eggs were found in the liver and intestines of the animals, but mainly in the liver. Signs of granuloma were present in the liver and in the intestines, but more pronounced in the liver. In this same study only one monkey from another species, *A. vociferans*, passed *S. mansoni* eggs at 8 weeks pi[33].

Our findings are similar to those of Warren *et al*[46]. While working with 9 marmosets (body weight 137-348g), 3 *C. jacchus* and 6 *C. penicillata*, 6 males and 3 females, infected percutaneously with 100 or 200 cercariae of a Brazilian *S. mansoni* strain per 100g of weight, they found hardly any *S. mansoni* egg in the marmoset feces, no clinical symptoms, no weight loss and on average the adult worms recovered amounted to 5.2% of the cercariae inoculated (1.9% to 10.5%). Worms were smaller than those usually recovered from infected mice, and the presence of other parasites co-infecting their animals. In animals infected with 100 cercariae, only one egg with a dead miracidium was found after 20 weeks of infection.

We conclude that when percutaneously infected with *Schistosoma mansoni*, SLM strain, the primate *C. jacchus* shows characteristics of non-permissiveness.

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