HEPATIC CAPILLARIASIS IN CHILDREN: REPORT OF 3 CASES IN BRAZIL

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Abstract. Capillaria hepatica is a helminth that may cause an extremely rare condition of parasitic hepatitis. Only 29 cases have been published, 2 of them in Brazil. We report here 3 cases of children in Brazil with massive hepatic capillariasis who presented the characteristic triad of this type of infection, i.e., persistent fever, hepatomegaly, and eosinophilia. The diagnosis was made by liver biopsy. All children responded well after treatment with thiabendazole (case 1), albendazole (case 3), and albendazole in combination with a corticoid (case 2). Case 1 has been followed-up for 24 years, an event not previously reported in the literature.

Capillaria hepatica, discovered in 1893 by Bancroft, is a nematode of the family Trichocephalidea and class Tricurida, the same as that of Tricuris trichiura. It is a habitual parasite found in the liver of rats, mice, dogs, cats, pigs, monkeys, and rabbits, with more than 40 mammalian species having been reported as hosts. Humans are an accidental host.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) The first case of human infection dates back to 1924\(^1\)\(^5\) and only 28 other cases have been reported,\(^4\)\(^5\)\(^7\)\(^10\)\(^11\) 2 of them in Brazil.\(^1\)\(^11\) The anatomicopathologic picture is that of parasitic hepatitis, with the formation of a granuloma around the eggs and the presence of focal necrosis.\(^1\)\(^4\)\(^8\)

Approximately 7–90% of rats (Rattus norvegicus) are naturally infected.\(^5\) In Brazil, the infection has been detected in 43% of the rats, being the most frequent helminthic parasitosis affecting rodents in São Paulo.\(^1\)

Capillaria hepatica infection may cause clinical signs and symptoms of varying intensity ranging from mild to severe, with a possible fatal outcome.\(^3\)\(^5\)\(^9\) Since this parasite is cosmopolitan and highly prevalent in rats, even domestic ones, it is believed that many human cases may go undetected and undiagnosed, thus explaining the small number of cases described.\(^1\)

The objective of the present paper is to report 3 new cases of hepatic capillariasis in children in Brazil diagnosed by liver biopsy and to report their respective clinical follow-up.

CASE REPORTS

Case 1. A 2-year-old boy from Jaboticabal, State of São Paulo, presented with cough and coryza over the past 90 days, which regressed with the use of cough syrups and penicillin. Since then, he had presented sporadic episodes of cough with expectoration and fatigue. Continuous mild fever with evening and night intensification, which regressed with medication, was noted in the last 70 days. The child simultaneously became paler, prostrated, with nocturnal sweating and reduced appetite. No weight loss was reported. He urinated more frequently, eliminating slightly dark urine. Discrete hepatosplenomegaly was observed 40 days before, gradually increasing in size, when the patient was referred to our service.

He habitually played near a collection of still water and had been bathing in a lagoon. Cats lived in the backyard of his home. His father had hepatitis 4 months before. His parents and 3 siblings are currently healthy.

A physical examination showed a weight of 12.6 kg, a height of 86.5 cm, fever, and a good general condition with generalized small mobile adenomegaly. The tonsils were hypertrophic and hyperemic, with purulent points. The lungs and heart were normal. The abdomen was globose, with visible collateral circulation. The liver was palpable 10 cm below the right costal margin and 5 cm below the xiphoid appendix, with a fine, soft, and painless border and with an irregular surface. The spleen was palpable 2 cm below the left costal margin.

Laboratory test results are shown in Table 1. Feces parasitology showed the presence of T. trichiura eggs. A chest radiograph was normal.

Histologic sections of the liver stained with hematoxylin and eosin showed a diffuse granulomatous process that completely distorted the parenchyma. The central region of these areas consisted of large amounts of eggs intermingled with cell debris. Epithelioid histiocytes and frequent multinucleated giant cells encircled these areas. Mononuclear inflammatory cells and abundant eosinophils were observed at the periphery (Figure 1, top). The bioperculated eggs were large and barrel shaped, with a thick external wall exhibiting striations. Internally, most eggs contained granular eosinophilic material. Partially degenerated eggs were frequent, with most of them located inside giant cells (Figure 1, bottom).

The child was treated orally with thiabendazole, 500 mg/day, for 3 days (Table 2). After a 2-year follow-up, a physical examination showed that the liver was palpable 1 cm below the right costal margin, with some palpable nodulations, and the spleen was not palpable. One year later, the liver was palpable 1 cm below the right costal margin and was of normal consistency. The spleen was not palpable. He was followed-up on an outpatient clinic basis for 6 years and 9 months without presenting any other alterations when he was discharged.

The patient is now 26 years old and is asymptomatic. After discharge, he reported only occasional asthma-like attacks up to 18 years of age and urolithiasis 4 years before. A current physical examination revealed no abnormalities, and the liver and spleen were not palpable. All current laboratory test results are within normal limits (Table 1). Results of an abdominal ultrasound examination were unremarkable, showing a liver of normal shape, contour, dimensions, and echogenicity.

Case 2. A 35-month-old girl born and living in Barretos,
State of São Paulo, complained of abdominal pain of medium intensity of 2-months duration localized in the right hypochondrium, with periods of improvement. She was treated with antiparasitic drugs after which she eliminated worms in the feces. The pain improved for about 3 days, returning later at a lower intensity. In addition to these symptoms, she started to have fever. Her parents also reported a productive cough, wheezing, respiratory discomfort, and moaning. The respiratory picture improved with medication but the fever and abdominal pain persisted. Forty days after the onset of symptoms, she passed dark yellow urine that stained her clothes, and presented yellowish skin. Her parents denied a history of hepatitis, sexually transmissible diseases, Chagas’ disease, or schistosomiasis. Cats and dogs were reported to be present in the backyard of her home.

Three weeks earlier, she had been hospitalized for 7 days with a diagnosis of pneumonia and had been apathetic since returning later at a lower intensity. In addition to these symptoms, she started to have fever. Her parents also reported a productive cough, wheezing, respiratory discomfort, and moaning. The respiratory picture improved with medication but the fever and abdominal pain persisted. Forty days after the onset of symptoms, she passed dark yellow urine that stained her clothes, and presented yellowish skin. Her parents denied a history of hepatitis, sexually transmissible diseases, Chagas’ disease, or schistosomiasis. Cats and dogs were reported to be present in the backyard of her home.

A physical examination showed a weight of 13 kg, a height of 95.6 cm, a regular general condition, mild paleness, moderate jaundice, fever (38.7°C), and no cyanosis. Cervical micropolyadeny and exulcerated lesions on the labial commissures were observed bilaterally. There was no respiratory tract abnormality. The abdomen was semi-globose, normotense, and painless, with visible collateral circulation. The liver was palpable 11 cm below the right costal margin and had a firm consistency. The spleen was percutaneous but not palpable.

Table 1 shows the results of relevant laboratory tests. Feces parasitology showed the presence of *Endolimax nana*. An ELISA for toxocariasis was reactive up to a 1/400 dilution.

An abdominal ultrasound examination showed hepatosplenomegalgy and discrete dilatation of intrahepatic bile ducts. A chest radiograph showed opacification of the right base of the lung. Abdominal computer tomography showed hepatosplenomegalgy with no clear evidence of adenomegaly. Nodules measuring less than 1 cm were observed adjacent to the aorta.

Histologic sections stained with hematoxylin and eosin showed a similar picture but much more intense with a higher amount of eggs (Figure 1, middle and bottom).

The child was treated with albendazole, 400 mg/day, for 100 days and with prednisone, 1 mg/kg/day, for 1 month, with a gradual decrease over a period of 75 days (Table 2). Twenty days after the beginning of treatment, there was general improvement with disappearance of the fever. During the two-year and four-month follow-up, the patient presented a palpable liver 2 cm below the costal margin and showed normal laboratory test results (Table 1).

**Case 3.** An 18-month-old girl born and living in Ribeirão Preto, State of São Paulo, had been refusing solid food for 2 months, accepting only a liquid diet and milk. During this period she started showing pica and ate wall paint, mud, brick powder, sofa foam stuffing, and paper. Fever started 5 weeks earlier (2–3 peaks/day), accompanied by wheezing. Three weeks earlier, she had been hospitalized for 7 days with a diagnosis of pneumonia and had been apathetic since then, with intermittent abdominal distention. Numerous pectechiae appeared 1 week before on the right lower limb. No vomiting, coughing, or urinary changes were reported. The family mentioned the presence of puppies, rats, and cats in their backyard. A physical examination showed a weight of 11.1 kg, a height of 79 cm. The patient was very pale, hydrated, eupneic, acyanotic, anicteric, and afebrile. A slightly rough vesicular murmur was present in the lungs, more reduced on the right base. The liver was palpable 6 cm below the right costal margin and the spleen was palpable 4 cm below the left costal margin.

Laboratory test results are shown in Table 1. A chest radiograph showed no opacification. A liver biopsy showed changes similar to those described for the other cases, with the detection of adult worms in the tissue (Figure 2).

The child was treated with albendazole, 400 mg/day, for

### Table 1

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Last follow-up visit</th>
<th>Case 2</th>
<th>Last follow-up visit</th>
<th>Case 3</th>
<th>Last follow-up visit</th>
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<td><strong>WBC</strong></td>
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<td><strong>Eo</strong></td>
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<td>61%</td>
<td>1%</td>
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<td><strong>Hb</strong></td>
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<td>9.7</td>
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<td>–</td>
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<td><strong>γGT</strong></td>
<td>–</td>
<td>21.2</td>
<td>8,322</td>
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<tr>
<td><strong>γ</strong></td>
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<tr>
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<td><strong>PT</strong></td>
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<td>INR = 1.1</td>
<td>INR = 1.7</td>
<td>INR = 1.0</td>
<td>INR = 1.3</td>
<td>–</td>
</tr>
</tbody>
</table>

*WBC = white blood cells; Eo = eosinophils; Hb = hemoglobin; TB = total bilirubin; DB = direct bilirubin; AP = alkaline phosphatase; BU = Bodansky unit; γGT = gammaglutamyl transpeptidase; γ = gammaglobulin; GOT = glutamate oxaloacetate transaminase; GPT = glutamate pyruvate transaminase; Alb = albumin; Glob = globulin; PT = prothrombin time; INR = international normalized ratio.

† For children.

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FIGURE 1. **Top,** low-power view of the needle biopsy of the first case. Note the granuloma with many eggs near the left upper corner. The architecture of the remaining parenchyma is preserved (hematoxylin and eosin stained, original magnification × 100). **Middle,** second case. The number of eggs per granuloma is higher than in the previous case (hematoxylin and eosin stained, original magnification × 100). **Bottom,** second case: high-power view of a granuloma. Note in the center the characteristic barrel-shaped bioperculated eggs showing a thick trilaminar capsule with striation of the outer layer. Multinucleated giant cells and epithelioid histiocytes compose the center of the lesion that is surrounded by mononuclear cells and polymorphonuclear eosinophils (hematoxylin and eosin stained, original magnification × 400).
Infection occurs after the ingestion of embryonated (infecting) eggs. The larvae hatch in the intestine, reaching the cecum, penetrating the mucosa, entering the tributaries of the vena portae, and reaching the liver. The larvae can be transported to the lungs, spleen, or to other organs, where, however, they do not develop, dying almost immediately. They mature and mate in the liver, producing millions of eggs. Approximately 40–60 days after infection, the adult worms die and disintegrate, releasing a large number of eggs that cause hepatic necrosis, an inflammatory reaction, and fibrosis. The eggs remain in the liver parenchyma without developing and are released into the environment only with the death and decomposition of the host. The three patients reported here presented respiratory alterations during the development of infection, probably due to the passage of larvae through the lungs or to bronchopneumonia associated with the granulomas.

Spurious infection occurs when the non-embryonated eggs present in the liver are ingested by a carnivore predator, simply crossing the gastrointestinal tract of the host and being excreted through the feces. It is important to point out that the ingestion of non-embryonated eggs does not cause liver disease but only transitory intestinal symptoms, with abdominal discomfort and vomiting.

Infection leads to hepatic capillariasis, which may vary from mild to severe in intensity. The symptoms are quite varied and are not present in all cases. Some of the more common signs and symptoms include the classical triad described above, plus splenomegaly, pneumonitis, fever, extreme weakness, constipation, abdominal distension, and sometimes ascites and malnutrition. The blood shows a microcytic hypochromic anemia, a moderate leukocytosis, hyperglobulinemia, and a particularly high eosinophilia averaging 77% (range = 56–85%). This type of infection seems to be rare in humans, since only 29 cases have been published worldwide thus far, 17 of them involving children between 1 and 5 years of age (94%). The higher incidence in this age range may be due to the more frequent soil-handmouth contact occurring at this age. Pica was reported in 3 of 14 children but not ruled out in the others. These facts are well illustrated in the three cases reported herein, with all showing a home environment favorable for the development of this infestation with the presence of cats, rats, and pica, a frequent finding among the poor children in our country, as reported in case 3. Our three patients presented a clinical picture of massive hepatic capillariasis and are consistent with the increased frequency of cases in this age range.

The diagnosis of capillariasis was determined by the histologic findings in the liver biopsy of the characteristic eggs of *C. hepatica*. The eggs of this helminth are elliptical in shape, bioperculated, ranging from 54 to 65 μm in length to 29 to 33 μm in width, present a double envelope, the inner one being thicker, with sagittal striae between them. These eggs are therefore considered to be geo-helminths.

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The livers of the 3 children in this study exhibited diffuse hepatic lesions similar to those reported in the literature, with the formation of many granulomas around the eggs, focal necrosis, eosinophilic infiltration, and fibrosis of varying intensity. All of these alterations were more intense in case 2. These lesions may evolve to cirrhosis, a fact that did not occur in cases 1 and 2. We were unable to define this possibility in case 3 since the patient was not followed up for a sufficient period of time. However, hepatosplenomegaly was still present on the occasion of her last visit. The formation of a solitary granuloma has also been reported, simulating a tumoral lesion.

Clinically, the infection requires differentiation from larva migrans (Toxocara canis, *T. cati*), amebic hepatitis, ascariasis of the liver, infectious hepatitis, pyogenic hepatitis, and diffuse infestation by *Strongyloides stercoralis*. Although *T. canis* is an parasite frequently found in Brazil, different types of worms may provoke closely similar signs and symptoms. A positive serologic test result for toxocariasis may represent a false-positive result due to a cross-reaction, as observed in patient 2; thus, investigations should continue to reach a more precise diagnosis. In the case of hepatic capillariasis, a definitive diagnosis can be made only by obtaining a liver biopsy or on the basis of autopsy results, since no immunodiagnostic method is currently available for etiologic elucidation, and the detection of eggs in the feces does not confirm the diagnosis since it only characterizes a spurious infection.

The 3 patients were treated with broad-spectrum anti-parasitic drugs, albenzadole in cases 2 and 3 and thiabendazole in case 1. These drugs only act on adult worms but are ineffective against the eggs, which will remain in the hepatic tissue, with maintenance of the lesion. Thus, in some cases it may be necessary to use corticosteroids to reduce the in-
Figure 2. Details of worms in the liver of the third case. Top, note the curved worm partially destroyed by the inflammatory process. There are some eggs inside the worm and others in the surrounding tissue (hematoxylin and eosin stained, original magnification ×100). Middle, oblique section of a worm. Note the thick center wall and two eggs inside the tissue (hematoxylin and eosin stained, original magnification ×400). Bottom, cross-section of a better preserved worm (hematoxylin and eosin stained, original magnification ×400).
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flammatoty response,\textsuperscript{5,11} as was done here for patient 2. In this case, the decision to use a corticoid was based on clinical, laboratory, and histologic signs of important aggression and inflammation in the liver. Cheetham and Markus, in an experimental study in mice, demonstrated that the separate use of albendazole, febantel, mebendazole, and oxendazole prevented ovipositing by \textit{C. hepatica} by more than 99\%.\textsuperscript{12} However, mebendazole was the only agent for which the dose used coincided with the therapeutic dose recommended for humans. Thus, these investigators concluded that mebendazole may continue to be the drug of choice for the treatment of human capillariasis.\textsuperscript{12} No side effects of the drugs and doses used were detected in the 3 patients in this study.

The diagnosis of capillariasis is quite difficult in most cases. Of the previous 29 cases published, only 7 survived, with death not necessarily due to hepatic involvement.\textsuperscript{5,10} The longest follow-up for the patients reported in the literature was 15 years.\textsuperscript{5} Patient 1 in the current study was followed-up for 24 years, a fact not previously reported in the literature. This patient is well and fully asymptomatic, both in terms of clinical and laboratory results, and can therefore be considered a case of a full cure. We do not know whether the cure was spontaneous or whether the 3 days of thiabendazole treatment were sufficient to promote it.

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