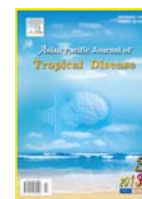




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Evaluation of cases with *Fasciola hepatica* infection: experience in 6 children

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PEER REVIEW

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Comments

The authors reported their experience with the fascioliasis including age, symptoms, specific diagnostic assays, treatment. The results of this article will lead the clinicians to think fascioliasis for non-specific symptoms associated with eosinophilia.

(Details on Page 215)

ABSTRACT

Objective: To evaluate 6 pediatric cases diagnosed as fascioliasis. **Methods:** Patients diagnosed as fascioliasis are retrospectively interpreted. **Results:** Herein 6 pediatric cases having a mean age of (12.7±3.1) years with different complaints including fever, weakness, paleness, sweating, cough, headache, rectal bleeding, abdominal pain, and abdominal distension admitting to our hospital are evaluated. **Conclusions:** Diagnosis of fascioliasis needs a high index of suspicion supported by stool microscopy, serology, imaging procedures, and in difficult cases even liver biopsy. Triclabendazole resistance should be kept in mind in unresponsive cases.

KEYWORDS

Fascioliasis, Turkey, Trematoda, Pediatric cases, Triclabendazole, Child

1. Introduction

Fascioliasis is an important chronic parasitic disease caused by two trematode liver fluke species: *Fasciola hepatica* (*F. hepatica*) and *Fasciola gigantica* (*F. gigantica*) infecting several mammalian species including cattle, goats, sheep, and humans^[1,2]. *F. hepatica*, a zoonotic helminth, has a cosmopolitan distribution especially in temperate zones, while *F. gigantica* is found in tropical regions of Africa and Asia^[3]. Infection occurs due to ingestion of water or

uncooked aquatic plants such as watercress contaminated with metacercariae, which exists in the intestine, perforates the intestinal wall, enters the peritoneum, and passes through the liver capsule to settle in the biliary tree^[2,4]. In the biliary tract, the mature fluke releases eggs, which are excreted in feces to complete the life cycle of parasite^[4]. The parasite usually infects the liver parenchyma and causes lesions, but rarely infects the extrahepatic tissues like brain and eye^[5,8]. The illness of fascioliasis consists of an acute phase, which causes the patient having fever,

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hepatomegaly, abdominal pain, eosinophilia, hemobilia, and hepatic nodules and a chronic phase which causes the patient having jaundice, angiocholitis, wasting, anemia, ascites, cardiac disorder, and pancreatitis[6,9,10]. In this report, we evaluated 6 children with different manifestations of fasciola infection.

2. Materials and methods

We evaluated 6 children admitting to Ankara Hematology Oncology Children's Training and Research Hospital as fascioliasis between January 2008 to October 2012. Data entry included age, duration and kind of symptom, physical examination, laboratory study, treatment and outcome of the patient. For the laboratory study of parasite, microscopic examination, serological examination and cultures of the specimens were performed. Patients diagnosed with *F. hepatica* with microscopic and serological examination were included in the study whereas one patient with a suspected fascioliasis with abdominal ultrasonography but unproven with serological test was excluded from the study.

SPSS 16 software was used for all analyses. Values are expressed as the mean±SD unless otherwise stated. $P < 0.05$ was considered statistically significant for all analyses.

3. Results

Six patients (three males, three females) between the age of 9 and 17 years [mean age: (12.7±3.1) years], with different complaints including fever, weakness, paleness, sweating, cough, headache, rectal bleeding, abdominal pain, and abdominal distension admitted to our hospital between November 2009 and June 2011. Mean duration of symptoms was 87.7 d (between 2 d and 1 year). Physical examination of the three patients revealed abdominal tenderness, hepatomegaly and pallor. However, other three had no signs in the physical examination. Half of the cases admitted to other centers before admission to our center and they had a story of drinking contaminated water. General characteristics of the patients were listed in Table 1.

In laboratory studies, mean hemoglobin was 11 g/dL; white blood cell count, $12 \times 10^9/L$; and platelet count of $397 \times 10^9/L$ respectively. Three children had a mild leukocytosis and thrombocytosis and one had significant leukopenia. Two patients had iron deficiency anemia. Peripheral blood smear revealed eosinophilia in all of the children and mean eosinophil ratio was 36%. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also evaluated. CRP values were negative or slightly increased in all cases. However, the ESR was high in most patients and the mean ESR was 36.8 mm/h. Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) were normal, except for a slight increase of AST and ALT in two patients. Only two patients serum immunoglobulin E levels were measured and one of them was approximately two times higher than the upper limit, while the other was 30 times higher than the normal values (Table 2).

Table 1
Characteristics of the patients.

Patient	Gender	Age (year)	Application time	Presenting symptom	Physical examination
1	Male	10	4 months	Abdominal pain and distension	Abdominal tenderness
2	Male	17	2 months	Fever, sweating, cough, headache	Normal
3	Male	9	1 month	Abdominal pain	Normal
4	Female	14	1 week	Weakness, paleness, headache	Hepatomegaly
5	Female	11	2 d	Weakness, paleness, fever	Paleness
6	Female	15	1 week	Rectal bleeding	Normal

Parasite examinations and cultures of stool were performed because of marked eosinophilia and possible parasitic diseases. There was no parasite eggs in stool of two children. However, one patient had *F. hepatica* eggs and the other one had *Hymenolepis. nana* (*H. nana*) eggs

Table 2
Laboratory findings of the patients.

Patient	WBC ($\times 10^9/L$)	Hg (g/dL)	Plt ($\times 10^9/L$)	Eo (%)	CRP (mg/dL)	ESR (mm/h)	IgE (IU/mL)	Liver functions
1	13.7	13.3	586	36	0.18	91	–	Slight increase in AST
2	17.4	15.5	246	72	1.24	45	30000	Normal
3	16.5	11.6	429	50	0.53	34	241	Slight increase in ALT
4	12.0	7.1	689	50	0.15	8	–	Normal
5	3.1	4.8	155	8	1.13	29	–	Normal
6	9.5	13.8	282	4	0.15	14	–	Normal

WBC: White blood cells; Hg: Hemoglobin; Plt: Platelet, Eo: Eosinophil; CRP: C-reactive protein (normal: 0–0.8); ESR: Erythrocyte sedimentation rate (normal: 0–20 in 1 h); IgE: Immunoglobulin E (normal: 0–100); AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Table 3

Evaluation of infectious agents in patients.

Patient	<i>T. gondii</i> IgM/IgG	<i>E. granulosus</i> IHA	<i>F. hepatica</i> IHA	<i>E. histolytica</i> IgM/IgG	<i>T. canis</i> IgM/IgG	Stool examination
1	-/-	-	1/1520	-/-	-/-	-
2	-/-	NE	1/5120	+/-	-/+	<i>G. lamblia</i> antigen (+), <i>B. hominis</i>
3	+/+	NE	1/640	-/-	NE	<i>G. lamblia</i> antigen (+), <i>H. nana</i> , <i>I. butschlii</i>
4	-/-	NE	1/312	-/-	-/-	-
5	-/-	NE	1/512	-/-	-/-	<i>F. hepatica</i>
6	NE	NE	1/320	-/-	NE	-

IgM: Immunoglobulin M; IgG: Immunoglobulin G; IHA: Indirect hemagglutination test; +: positive; -: negative; NE: not examined.

in direct examination of stool. One of the patients was positive for Giardia antigen and the other was positive for *Blastocystis hominis* (*B. hominis*) eggs, *Iodamoeba butschlii* (*I. butschlii*) cysts and *Giardia lamblia* (*G. lamblia*) antigen. Serological examination was also performed for all patients with possible parasitic diseases. In some patients, *Toxoplasma gondii* (*T. gondii*) and *Toxocara canis* (*T. canis*) were detected in serological studies by ELISA. At the same time, some parasites including *Echinococcus granulosus* (*E. granulosus*) and *Entamoeba histolytica* (*E. histolytica*) were excluded with these studies. The only serological finding that are common for all children was positive indirect hemagglutination (IHA) test for *F. hepatica* at different titrations of between 1/312 and 1/5120 (Table 3).

Two patients had signs of infection for five different parasites at the same time. The patients with multiple parasites were evaluated for immune deficiency diseases, but none of them had primary immune deficiency.

Abdominal ultrasonography was performed for all patients positive IHA tests for *F. hepatica*. Although two patients had normal abdominal ultrasonography findings, all the others had different changes in liver parenchyma and concomitant lymph nodes, enlarged in different locations of abdomen (Table 4).

Table 4

Abdominal ultrasonography findings.

Patient	Images
1	The left lobe of the liver included a cystic lesion; 11 mm ×7 mm in diameter; with septations and mural nodular appearance and multiple millimetric hypoechoic lymph nodes; the largest one was 10 mm×5 mm in size; located parailiac, paraaortic and mesenteric region.
2	In the right liver lobe, subcapsular selected peripheral hyperechoic focus and uncertain contoured hypoechoic area plan; 50 mm×35 mm in size; also located adjacent to the liver and vascular structures.
3	Compatible with peliozis hepatis
4	Lymph nodes at the hilus of the liver; the largest one was 15 mm×5 mm in size; and multiple millimetric hypoechoic ovoid lymph nodes; the largest one was 13.0 mm×5.5 mm in size; located at parailiac, paraaortic and mesenteric region.
5	No pathological appearance
6	No pathological appearance

Eventually, 5 children diagnosed as having *F. hepatica* by serologically or stool examination were treated with triclabendazole at a dosage of 10 mg/kg per day orally for 3 consecutive days and this treatment was repeated after 10 d. One patient was positive for *F. hepatica*, IHA and *E. histolytica* ELISA tests at the same time and was treated with oral metronidazole for two weeks. However, this patient was unresponsive to treatment because of persistent symptoms and had positive serum PCR tests for *F. hepatica* and *T. canis* after metronidazole cure. This patient had subcapsular hypoechoic lesion with 66 mm×55 mm diameter and uncertain contours in posterior segment of right liver lobe in the abdominal ultrasonography after treatment. Abdominal magnetic resonance showed hepatosplenomegaly with capsular peripheral wedge-shaped and not clear contoured lesion, 67 mm×70 mm×95 mm in size at the right lobe of liver, with spherical lymph node at portal hilum about 20 mm×30 mm in size and heterogeneous enhancing focal area, 25 mm in diameter and multiple millimetric foci at upper pole of the spleen after metronidazole cure. Thoracic computed tomography and eye examination were performed because of positive PCR for *T. canis*, which were normal. Albendazole treatment for *T. canis* and triclabendazole for *F. hepatica* were initiated for this patient. After triclabendazole treatment, titration of the *F. hepatica* IHA levels decreased, eosinophilia returned to normal levels, and symptoms related to the parasitic infection improved within a few months. In one patient, abdominal pain and a significant increase in liver function tests was observed for approximately two months after initiation of therapy. Abdominal ultrasonography of the case showed a cystic lesion with septations, 11 mm×8 mm in size in the left medial lobe of liver. The patient was treated with triclabendazole for the second time. Liver function did not return to normal levels with the second cure and liver biopsy was performed; which resulted in chronic hepatitis.

4. Discussion

Fascioliasis is a zoonosis caused by *F. hepatica* and less commonly *F. gigantica*, distributed in some countries such as Spain, France, Germany, Great Britain, Bolivia,

Iran, Peru, Austria, Norway, United States, Portugal, China and Turkey^[6,9,11,12]. *F. hepatica* is a flat and leaf-shaped trematode. It's life cycle consists of 7 stages including egg, miracidium, sporocyst, redia, cercaria, metacercariae, and adult fluke. The parasite has two hosts of intermediate and definitive hosts. Mammals like sheep, goats, and cattle are usually definitive hosts and infected by ingesting metacercariae form^[5,12,13]. Human, the accidental host, get the disease by drinking contaminated water with metacercariae, eating watercress, lettuce, alfalfa or spinach plants, and using contaminated kitchenware^[3,6]. Only half of our cases had suspicious history of drinking contaminated water, whereas there was no history about disease transmission in the others.

The metacercariae excyst in the small intestine, penetrate the intestinal wall, move into the peritoneal cavity, and invade into the liver parenchyma through the capsule. About six weeks later, the parasites settle down in the biliary tract where they become mature and produce eggs that are excreted with stools^[6,12,13]. If the larvae accidentally lose their own way to the liver; they reside in the other organs or systems and cause ectopic fascioliasis^[6]. The disease includes 4 clinical periods: (1) Incubation phase, from the ingestion of metacercariae to the first symptoms; (2) Acute phase, migration of the fluke to the bile ducts, with symptoms of fever, abdominal pain, respiratory symptoms, gastrointestinal disturbances, hepatomegaly, splenomegaly, ascites, anemia, and jaundice; (3) Latent phase, maturation of the parasites and starting of oviposition with eosinophilia, gastrointestinal complaints and relapses of acute symptoms; (4) Chronic phase with bile duct obstruction, cholecystitis, cholangitis, liver abscess, hemorrhage, lithiasis, and cirrhosis. The chronic stage may be asymptomatic and extended for years if the disease remains untreated^[14,18]. Our patients were compatible with the acute phase in terms of symptoms, but some were in the latent phase due to eosinophilia and the laboratory findings. The highest level of eosinophilia is determined in the last period of acute phase and the beginning of the chronic phase^[19].

According to the literature, laboratory studies generally demonstrate anemia and leukocytosis, but hyperleukocytosis is very rare. Immunoglobulin levels may be elevated, especially IgE, as observed in our two patients^[20,21]. Anemia was also observed in our two cases. Furthermore, low levels of CRP in all our patients and high ESR of four patients supported the knowledge that fascioliasis is a chronic infection.

Fascioliasis is difficult to diagnose on admission, because it is uncommon. After the disease is clinically suspected, diagnosis should be confirmed with the appearance of *F. hepatica* egg by a parasitologist in the feces. However, stool examination alone may not be enough for the diagnosis in all stages of the infection, because the parasite cannot produce eggs before invasion of biliary tract^[22]. Besides examination

of stool, serological tests as indirect hemagglutination are more valuable for diagnosis and can be used in all stages, including the acute stage when the eggs are not excreted in the feces yet, and in the evaluation of the treatment outcome^[6,23]. In this study, only one patient's stool examination was positive for *F. hepatica* eggs, while IHA tests of all patients were positive. Because, all our patients were in acute or latent phase and the eggs were not excreted in the feces yet.

Two of our patients had signs of infection for five different parasites at the same time including *G. lamblia*, *B. hominis*, *H. nana*, *I. butschlii*, *E. histolytica*, *T. canis* and *T. gondii*. Marcos *et al.* showed that children may have more than one intestinal parasites, such as, in descending order of prevalence: *G. lamblia*, *Ascaris lumbricoides* (*A. lumbricoides*), *E. histolytica*, *H. nana*, *Trichuris trichiura*, *Enterobius vermicularis* and *Strongyloides stercoralis*^[19]. In the same study, one child had seven species of intestinal parasites and only *A. lumbricoides* infection was associated with *F. hepatica* among these different species of intestinal parasites.

Radiological examinations are very useful in the diagnosis of fascioliasis. The movement of parasite in the gall bladder and liver lesions formed by the organism can be detected by ultrasonography. Although not specific, diagnostic ultrasonography findings of fascioliasis include heterogeneity of the liver by multiple, scattered, poorly defined hypo-isoechoic lesions, periportal lymph node enlargement, dilatation of the common bile ducts or intrahepatic biliary channels and thickening of the gallbladder and echogenic, non-shadowing multiple particles in the gallbladder or in the common bile ducts. Similarly, in studies of contrast-enhanced CT and MRI, specific views suggestive of fascioliasis can be detected^[24,28]. While ultrasonographic images of our four patients were compatible with fascioliasis, two patients showed normal abdominal ultrasonography.

Triclabendazole at a dosage of 10 mg/kg per day, orally; is the most effective drug for treating liver fluke infections in both acute and chronic phases. The course of treatment should be repeated after a certain period. Metronidazole, chloroquine, praziquantel, albendazole, and bithionol are the alternative drugs for *F. hepatica* infection^[29,31]. We treated our cases with triclabendazole with two cycle of treatments. This treatment was used in a patient after metronidazole therapy was unsuccessful. Albendazole and triclabendazole treatments were used together in one of patients. There was a complete response for all patients having received this treatment, whereas recurrence occurred in one patient due to triclabendazole resistance.

F. hepatica is not seen rarely, whereas this infection may be overlooked in Turkey. Fascioliasis is an important public health problem and should be considered in children with non-specific symptoms and significant eosinophilia. If the disease is suspected strongly, serological tests should also

be performed in cases with normal stool examination.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Fascioliasis is an important chronic parasitic disease localized at different localization of world and have wide spectrum of symptoms including fever, hepatomegaly, abdominal pain, eosinophilia, hemobilia, hepatic nodules, jaundice and angiocholitis.

Research frontiers

Studies are performed to estimate the prevalence of fascioliasis in Turkey and Asia. Challenging process of diagnosis and differential diagnosis became easier with the help of these studies.

Related reports

Several reports including patients with fascioliasis from Spain, France, Germany, Great Britain, Bolivia, Iran, Peru, Austria, Norway, United States, Portugal, China and Turkey were reported. The parasite has two hosts of intermediate and definitive hosts. Mammals like sheep, goats, and cattle are usually definitive hosts and infected by ingesting metacercariae form while human, the accidental host, get the disease by drinking contaminated water with metacercariae, eating watercress, lettuce or spinach plants, and using contaminated kitchenware.

Innovations & breakthroughs

This study had focused on fascioliasis and challenging process of diagnosis and differential diagnosis, since it has non-specific symptoms except significant eosinophilia.

Applications

The results of this research was applied in differential diagnosis.

Peer review

The authors reported their experience with the fascioliasis cases. The results of this article will lead the clinicians to consider fascioliasis for non-specific symptoms associated with eosinophilia.

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