Fasciola hepatica infection: clinical and radiological findings in pediatric patients

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SUMMARY: Karadağ-Öncel E, Özsürekçi Y, Özkaya-Parlakay A, Çelik M, Cengiz AB, Haliloğlu M, Ceyhan M, Kara A. *Fasciola hepatica* infection: clinical and radiological findings in pediatric patients. Turk J Pediatr 2012; 54: 362-367.

Fascioliasis, an uncommon liver disease in children, is caused by the trematode *Fasciola hepatica*. Its clinical and laboratory findings may mimic several disorders of the liver, including malignancies. Diagnosis is usually made by demonstrating the presence of the parasite in liver tissue or the stool, or by serology, but many children are diagnosed incidentally. Described here are the clinical, laboratory and radiological features of five pediatric fascioliasis cases with different clinical pictures presenting over a period of five years, all of whom were successfully cured with oral triclabendazole.

Key words: Fasciola hepatica, child, clinical and radiological findings.

Fascioliasis is a worldwide zoonotic disease caused by the trematode liver fluke *Fasciola hepatica (F. hepatica)*. An estimated 17 million people are believed to be infected, with another 91.1 million at risk for infection[1]. *F. hepatica* is particularly endemic in Eastern Europe, South America and North Africa[2-4]. Studies from Turkey have reported a frequency of 0.03-0.8% for *F. hepatica* infections[5].

Children are usually affected more commonly than adults[4,6], while infections tend to run a more severe course in females, with a higher frequency of liver or biliary complications[4,6,7].

The trematode primarily infects sheep, goat, cattle, and other ruminants. Transmission to human beings, who are accidental final hosts, occurs after ingestion of aquatic vegetation such as watercress or by drinking water contaminated with metacercariae[2,8]. After the initial infection, oviposition takes place within 3-4 months, and adult flukes have a life span of up to 10 years[2,9].

Typically, clinical findings manifest after the parasite settles in the liver[10]. Although two clinical phases of fascioliasis have been recognized in humans, it is often difficult to diagnose and distinguish between them. The acute phase is associated with larval migration to the liver, and lasts 1-3 months after ingestion of metacercariae. The chronic phase, which may span several years, begins when the adult flukes reach the bile ducts. Nearly half of the patients may be asymptomatic during the chronic phase[11]. In recent years, several reports have described cases with mixed-phase fascioliasis[10,12].

With this report, we attempted to share our experience with fascioliasis in five children over a period of five years, including a description of associated signs and symptoms as well as laboratory and radiological findings.

Material and Methods

This retrospective study was undertaken by the Department of Pediatric Infectious Diseases at the Faculty of Medicine of Hacettepe University. The medical records of patients diagnosed with *F. hepatica* infection between July 2005 and October 2011 were systematically reviewed. Relevant information such as demographics as well as clinical, laboratory and radiological findings was recorded on pre-prepared forms. All laboratory tests had been performed in our local laboratory, and all patients were subjected to abdominal ultrasonography, with or without a computed tomography (CT). For the purpose of this study, all films that were available within the digital database of the hospital were reevaluated by an experienced designated radiologist.

Results

Demographic, Epidemiological and Clinical Features

During the period spanning July 2005 and October 2011, 5 patients (3 males, 2 females) with a mean age of 11.4 years were diagnosed with *F. hepatica* infection. An immunodiagnosis was made in all patients using indirect (passive) hemagglutination (IHA) assay, which was performed at the Refik Saydam National Public Health Agency, or by an ELISA test that detects antibodies against excretory-secretory antigen products from adult *F. hepatica*.

While 3 patients (60%) were city-dwellers, the remaining 2 patients (40%) were from rural areas. Two patients (40%) gave a history of ingesting aquatic vegetation. Three patients (60%) presented during the summer months, whereas the other two were diagnosed in winter (40%). Only 1 patient (20%) had a family history of *F. hepatica* infection.

The most frequently reported presenting symptom was fatigue/malaise (100%), followed by abdominal pain (80%), nausea and vomiting (60%), weight loss (40%), and cutaneous findings (40%). Of the 4 patients with abdominal pain, the pain in 2 of them (50%) was localized to the right hypochondrium, while 1 patient each (25%) had either left hypochondrial or epigastric pain. Other presenting symptoms of note included fever (20%), arthralgia (40%), cough (40%), myalgia (20%), and headache (20%). With regard to physical findings, 2 patients (40%) had hepatomegaly while 1 patient (20%) had splenomegaly. Findings on physical examination were unremarkable in 3 patients (60%). Demographic, epidemiological and clinical features of the patients are summarized in Table I.

Laboratory and Radiological Findings

A review of laboratory results revealed the patients to have a mean hemoglobin concentration of 13.5±2.3 g/dl and a leukocyte count of 23.04±15.98 cells/μl with marked eosinophilia (15.1±14.39 cells/μl). Mean values for the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) were 33.8±11.1 (<34) U/L, 35.6±8.1 (<35) U/L, 24.7±17.4 (<45) U/L, and 234.8±93 (<390) U/L,

Table I. Demographic, Epidemiological and Clinical Features in Cases of Fascioliasis

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	6	14	10	17	10
Gender	Male	Male	Female	Male	Female
History of ingesting aquatic vegetation	-	-	+	+	-
Place of dwelling	Urban	Urban	Rural	Rural	Urban
Season of presentation/year	Winter/2010	Summer/2008	Summer/2005	Summer/2010	Winter/2007
Family history of fascioliasis	-	-	+	-	-
Clinical features					
Abdominal pain	+	-	+	+	+
Localization of pain	Left hypochondrium	-	Right hypochondrium	Right hypochondrium	Epigastric
Fever	-	-	+	-	-
Nausea and vomiting	-	-	+	+	+
Weight loss	-	-	+	+	-
Fatigue/malaise	+	+	+	+	+
Cutaneous findings	-	Generalized pruritus	-	Generalized pruritus	Urticarial rash
Other	Arthralgia	Myalgia	Cough, Arthralgia	Cough, Headache	None
Physical examination	Hepatomegaly, Splenomegaly	None	None	None	Hepatomegaly

respectively. In terms of liver function tests, the patients had a mean international normalized ratio (INR) of 1.1±0.06 (0.86-1.20), with a serum albumin concentration of 4.5±0.01 (3.8-5.4) g/dl. Although all patients had elevated serum immunoglobulin (Ig)E levels (mean: 3236±4505 IU/ml, median: 1310 IU/ml, normal range: 0-52 IU/ml), examination of repeat stool samples did not reveal any signs of a parasitic infection. A diagnosis was confirmed in 1 patient using IHA, while for the remaining 4 patients, the ELISA method was used.

Ultrasonographic examination revealed the presence of hypoechoic lesions in the liver of all patients, with heterogeneity of the liver parenchyma in 2 patients (40%) and signs of elevated portal pressure on Doppler ultrasound in 1 patient (20%). A CT scan was obtained for 3 patients, showing multiple hypodense lesions in the liver (Figs. 1, 2). Laboratory and radiological findings of the patients are summarized in Table II.

Treatment and Follow-Up

All patients were started on 10 mg/kg/day of triclabendazole, as a single dose or in two divided doses. While 4 patients responded to a one-month course of triclabendazole, 1 patient required treatment for two months because the lesions persisted on ultrasonographic examination. Adverse effects to treatment (fever and abdominal pain) were observed in 3 patients (60%). Disappearance of lesions was confirmed on ultrasonographic follow-up in all of the patients after the triclabendazole treatment.

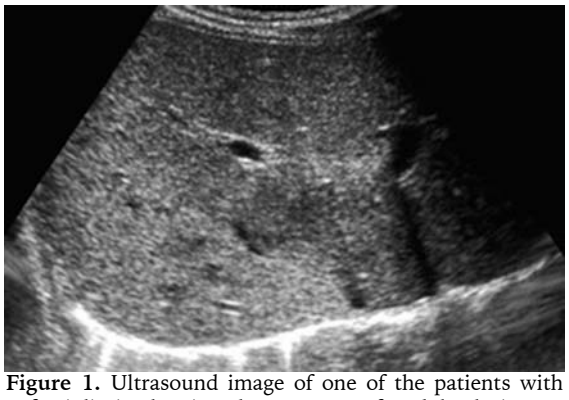

Figure 1. Ultrasound image of one of the patients with fascioliasis showing the presence of nodular lesions with undefined margins having both iso- and hypo-echoic characteristics in the posterior segment of the right hepatic lobe.

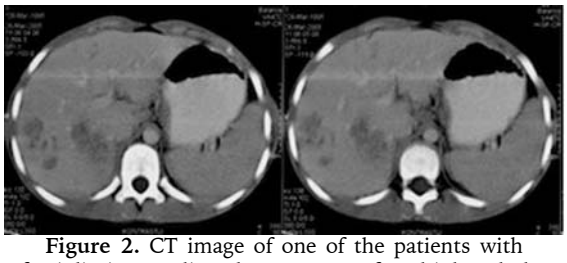

Figure 2. CT image of one of the patients with fascioliasis revealing the presence of multiple tubular branching and nodular lesions with irregular margins in the posterior segment of the right hepatic lobe.

Discussion

Hepatobiliary fascioliasis is sporadic in Turkey, and is usually recognized incidentally during surgical or endoscopic procedures in adults. Childhood hepatobiliary fascioliasis is rare, and patients may present with varying symptoms mimicking other hepatobiliary disorders. Common findings during the acute phase include prolonged fever, abdominal pain, anorexia, weight loss, nausea and vomiting, cough, diarrhea, urticaria, pruritus, lymphadenopathy, and arthralgia[6,11,13]. Splenomegaly, ascites, subcapsular hepatic hematoma, intra-abdominal hemorrhage, and pericardial and pleural effusion have also been reported[9,13]. Symptoms encountered in the chronic phase are generally related to biliary obstruction, such as upper abdominal pain, intermittent jaundice and intrahepatic cystic abscesses with prolonged fever[11,14,15]. The frequencies of presenting symptoms observed in our patient group - abdominal pain (80%), fever (20%), fatigue/malaise (100%), weight-loss (40%), and nausea and vomiting (60%) - are similar to previous adult reports[16], and none of our patients had intermittent jaundice, different from adult reports[11]. Occasionally, juvenile larvae may migrate to other anatomic locations such as subcutaneous tissue, the eyes, pancreas, central nervous system, and stomach wall, among others[9,17], resulting in a variety of symptoms depending on the involved organ. None of our patients had an ectopic infection.

While mild-to-moderate eosinophilia may be considered a typical finding during the acute phase of an *F. hepatica* infection[8], hypereosinophilia mimicking leukemia is very

Table II. Laboratory and Radiological Findings in Cases of Fascioliasis

Findings	Case 1	Case 2	Case 3	Case 4	Case 5
Hemoglobin, g/L	156	148	107	151	113
Leukocyte count, 10^9/L	50600	18700	20600	16000	9300
Eosinophil count 10^9/L	40400	7100	12770	9600	5670
Relative eosinophil count (%)	80	38	62	60	61
ALT (U/L)	36	37	36	45	15
AST (U/L)	45	39	34	37	23
GGT (U/L)	17.5	12.5	34	50.9	9
ALP (U/L)	203	215	246	128	382
Total/direct bilirubin (mmol/L)	4.95/0.17	5.81/0.51	7.86/1.53	6.32/0.34	6.32/1.02
Prothrombin time (INR)	1.2	1.04	1.1	1.06	1.1
Serum albumin (g/L)	46.4	45.6	44.7	43.5	45.1
IgE (mg/L)	16480	13100	10340	112810	9100
Stool examination	-	-	-	-	-
IHA/ELISA	1/2560	+	+	+	+
Ultrasound	Hepatomegaly with linear hypoechoic strains, splenic enlargement and increase in portal venous pressure	Hypoechoic strains in right lobe of the liver	Heterogeneously increased liver density, hypoechoic strains in right lobe of the liver	Hepatomegaly with linear hypoechoic strains, heterogeneously increased liver density	Linear hypoechoic strains
CT	-	Several hypodense lesions with irregular borders in posterior segment of right lobe	Hypodense lesions with irregular borders in posterior segment of right lobe	-	Several hypodense lesions with irregular borders in posterior segment of liver

rare. In a study from Egypt on 40 children with *F. hepatica*, the authors reported on an eosinophil count between 0.9-21 x 10^9/L[18]. Leukocytosis is another laboratory finding commonly associated with fascioliasis. In a study by Mailles et al.[19], leukocytosis was observed in 77.7% of the patients. Severe eosinophilia (>5x 10^9/L) was detected in all our patients, with Case 1 having marked hypereosinophilia. Hypergammaglobulinemia and anemia are two other presenting features of acute fascioliasis[8]. Two of our patients (40%) had anemia, whereas elevated IgE levels were detected in all patients.

Elevations in ALT and AST levels during the acute phase suggest the presence of hepatic inflammation, reflecting the severity of the initial illness. Levels gradually decrease in the chronic phase. Total bilirubin, GGT and ALP elevations are indicative of extrahepatic cholestasis, and are encountered more frequently in the chronic phase[20]. Liver enzyme levels were normal or near normal in all our patients.

Radiological imaging modalities are essential diagnostic tools in patients with a suspected *F. hepatica* infection[21]. Findings on ultrasonography, CT or magnetic resonance imaging (MRI) are commonly misdiagnosed as malignancies. Ultrasonographic findings include hepatomegaly, minimal parenchymal irregularity, focal areas of increased echogenicity, multiple nodular or irregular lesions of variable echogenicity, or a

single complex mass in the liver resembling a malignancy[9,22]. On CT, *F. hepatica* infection may appear as multiple, small, indiscrete, hypodense lesions ranging in size from 2-10 mm and microabscesses arranged in a tunnel-like and branching pattern located just under the capsule[23]. Such hypodense lesions on CT scans appear hypointense in T1-weighted MRI images and hyperintense in T2 images[24]. The radiological characteristics of these lesions are shared by liver metastasis, which makes a distinction very challenging. All our patients had undergone ultrasonographic evaluation, while a CT was required to confirm a diagnosis in three patients.

Although not pathognomonic, histopathological findings on a liver biopsy include leukocyte (PMNL) infiltration with excess eosinophils, necrotic debris, track-like destruction of parenchyma, fibrosis, and bile duct proliferation[25]. A liver biopsy was not deemed necessary in any of our patients, as clinical, laboratory and radiological findings were sufficient for the diagnosis.

Fascioliasis should always be considered in the differential diagnosis in patients with findings suggesting the presence of a hepatobiliary disorder who dwell in endemic areas and give a history of ingesting aquatic vegetation. However, lack of such a history does not necessarily rule out infection, since there is mounting evidence that an infection can be acquired by drinking contaminated water[26]. Only two of our patients (40%) gave a history of ingesting aquatic vegetation. In some countries where fascioliasis is endemic, seasonality has been observed[27], with Faraq et al.[28] reporting higher transmission rates in summer. In our study, 60% of the patients presented in summer, while 40% were diagnosed during the winter months.

Triclabendazole is the drug of choice for the treatment of both phases of *F. hepatica* infection[29]. The recommended daily dose is 10 mg/kg, and in case of treatment failure, varying success has been reported with 20 mg/kg twice a day[14]. Apt et al.[30] reported a cure rate of 79.2% after one course and of 100% after a second course. One month of treatment was sufficient in four of our patients (80%), while a second course was deemed necessary in only one patient (20%). Although triclabendazole is a safe and effective anti-parasitic, several side effects such as dizziness, headache, fever, and abdominal pain have been reported to occur 5-6 days after initiation of treatment[31]. At least one adverse effect was observed in three of our patients (60%).

Examination of the stool for *F. hepatica* ova may be of some use during the acute phase, since parasites cannot produce eggs before invading the biliary tract[32]. In the chronic phase, the diagnostic yield of the microscopic examination of the stool is low. Stool examinations were not helpful in the diagnosis in any of our patients.

Many characteristics of *F. hepatica* infections are shared alike by children and adults. Patients in the pediatric age group may be diagnosed incidentally while being investigated for seemingly unrelated symptoms, a point highlighted by our study results. Fascioliasis should be strongly considered in the differential diagnosis of patients with leukocytosis, hypereosinophilia and hypoechoic lesions on abdominal ultrasonography.

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