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Fasciola hepatica Infection: Demographic, Radiological, Laboratory Findings and Their Role in Acute and Chronic Differentiation

Fasciola hepatica İnfeksiyonu: Demografik, Radyolojik, Laboratuvar Bulguları ve Akut-Kronik Ayırımındaki Rolü

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ABSTRACT

Introduction: *The aim of this study was to investigate demographic, radiological and laboratory features of Fasciola hepatica infection and to determine its effects on acute and chronic differentiation.*

Materials and Methods: *Patients with F. hepatica; and their demographic data such as age, sex, place of residence, and serological tests of F. hepatica, leucocyte, hemoglobin, platelet, eosinophil, AST, ALT, GGT, ALP, bilirubin, amylase were evaluated retrospectively. The presence of characteristic findings in radiology and/or F. hepatica IgG positivity in acute phase and endoscopic retrograde cholangiopancreatography revealed F. hepatica extraction as chronic phase. Retrograde cholangiopancreatography and radiological findings were evaluated retrospectively.*

Results: *A total of 17 patients, 1 (5.9%) male and 16 (94.1%) female, were included into the study. Mean age was 46.18 (min-max: 24-83) years. Of the cases, 10 (58.8%) were acute, 7 (41.2%) were chronic, and 9 (52.9%) were settled in rural and 8 (47.1%) in urban areas. In 10 (58.8%) cases, eosinophils were higher than 5% and normal in the others. In ultrasonography, 7 (40.9%) were normal, 7 (40.9%) had hypoechoic lesions, and 3 were defined as gallbladder F. hepatica. When compared to acute and chronic F. hepatica; median age was 45.5 (24-83) years and 46 (32-57) years respectively (p= 0.961). There was no significant difference in laboratory data for AST, ALT, GGT, ALP, bilirubin, eosinophil, CRP (p> 0.005). Albumin was 4.6 g/dL, 3.9 g/dL (p= 0.009), and platelet count were 300 x $10^3/\mu L$ (p= 0.004) and 221 x $10^3/\mu L$ respectively.*

Conclusion: *Female gender and the presence of eosinophili are the findings that increased susceptibility to F. hepatica. Laboratory data for acute and chronic differentiation were not helpful but albumin and platelet levels were significantly lower in chronic cases. There is a need for prospective studies involving more cases.*

Key Words: *Fasciola hepatica; Acute; Chronic; Eosinophilia; Endoscopic retrograde cholangiopancreatography*

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ÖZ

Fasciola hepatica İnfeksiyonu: Demografik, Radyolojik, Laboratuvar Bulguları ve Akut-Kronik Ayırımındaki Rolü

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Giriş: *Bu çalışmada amaç, Fasciola hepatica infeksiyonunun demografik, radyolojik ve laboratuvar özelliklerini araştırmak ve akut-kronik ayırımındaki etkilerini saptamaktır.*

Materyal ve Metod: *F. hepatica tanılı hastaların yaş, cinsiyet, yaşadığı yer gibi demografik verileri, F. hepatica serolojik testleri, lökosit, hemoglobin, platelet, eozinofil, AST, ALT, GGT, ALP, bilirubin, amilaz gibi laboratuvar verileri retrospektif incelendi. Radyolojik olarak karakteristik bulguların varlığı ve/veya F. hepatica IgG pozitifliği, akut faz, endoskopik retrograd kolanjiyopankreatografide F. hepatica ekstraksiyonu ise kronik faz olarak değerlendirildi. Retrograd kolanjiyopankreatografi ve radyoloji bulguları retrospektif elde edildi.*

Bulgular: *Çalışmaya 1 (%5.9)'i erkek, 16 (%94.1)'sı kadın toplam 17 hasta dahil edildi, yaş ortalaması 46.18 (min-max: 24-83) yıl idi. Olguların 10 (%58.8)'u akut, 7 (%41.2)'si kronik olup, 9 (%52.9)'u kırsal, 8 (%47.1)'i kent yerleşimli idi. Olguların 10 (%58.8)'unda eozinofil sayısı %5'ten yüksek, diğerlerinde normaldi. Ultrasonografilerin, 7 (%40.9)'si normal, 7 (%40.9)'si hipoekoik lezyon, üçü safra kesesinde F. hepatica olarak sonuçlanmıştı. Akut ve kronik F. hepatica karşılaştırıldığında sırasıyla yaş ortalamaları median 45.5 (24-83) yıl ve 46 yıl (32-57) (p= 0.961) idi. Laboratuvar verileri AST, ALT, GGT, ALP, bilirubin, CRP açısından anlamlı fark yoktu (p> 0.005). Albumin akut ve kronik F. hepatica'da sırasıyla 4.6 g/dL ve 3.9 g/dL (p= 0.009); platelet sayısı 300 x 10^3/μL ve 221 x 10^3/μL (p= 0.004) olup fark istatistiksel olarak anlamlıydı.*

Sonuç: *Kadın cinsiyet, eozinofili varlığı, F. hepatica şüphesini artıran bulgulardır. Akut-kronik ayırımında laboratuvar verileri pek yardımcı olmasa da albumin ve platelet değerlerinin kronik olgularda daha düşük olması bu konuda daha çok olgunun dahil edildiği prospektif çalışmalara ihtiyaç olduğunu göstermektedir.*

Anahtar Kelimeler: *Fasciola hepatica; Akut; Kronik; Eozinofili; Endoskopik retrograd kolanjiyopankreatografi*

INTRODUCTION

With its intermediary host being molluscs, *Fasciola hepatica* is observed commonly among animals like sheep, goats, and cattle. *F. hepatica* is a parasite from the fasciolidea family in the trematode class transmitted through the ingestion of watercress, green vegetables, freshwater plants or of water containing metacercariae[1]. Eggs shed with the mammal faeces will only continue their development if they reach freshwater of appropriate environmental characteristics and if climatic conditions are suitable (15-25°C), the miracidia develop, and it infects snail. The parasite proliferates and after about 6 weeks, the cercariae is released. Cercariae forms infective metacercariae on green plants. With the ingestion of these herbs, metacercariae passes through the intestinal wall into the peritoneal cavity and reaches the liver parenchyma through the liver capsule. Immature parasites turn into mature parasites in 6-8 weeks before they enter the bile ducts, and begin to produce detectable eggs in the feces[2,3].

The infection occurs in two clinical periods, namely the acute phase covering the stage of hepatic invasion and the chronic phase with the parasite involving the biliary tracts[4,5]. The clinical symptom of acute infection depends on the damage caused by the larvae and the inflammatory response to it. Eosinophilia and IgE elevation are frequently observed as laboratory findings[6]. Chronic stage is characterized by adult parasite living in the hepatic and main bile ducts of the host. Patients are often asymptomatic at this stage. In rare cases, mucosal erosion associated with biliary obstruction, ascending cholangitis, acute pancreatitis or hemobilia may occur in infected individuals[7].

Despite restrictions on the climatic and environmental conditions, *F. hepatica* has spread to 5 continents from the near eastern geog-

raphical region where it is endemic[3]. Fasciola contamination foci are in patchy distribution. Its prevalence in humans is related to the distance to water resources, which are the source of fasciola[3]. The prevalence of *F. hepatica* has been reported to be 6.7 to 47.4% (average: 24.4%) among humans in hyper endemic regions[8]. The *F. hepatica* infection may occur after travels to high-risk endemic regions including the Nile Delta in Egypt, Iran, Turkey, Southeast Asia, Mexico, the Caribbean, and Andean Altiplano[9]. The seroprevalence has been specified to be 2.78% in the eastern part of Turkey[10].

The parasite is definitively diagnosed upon the identification of parasite eggs in stool or duodenal aspirate. However, this method offers a low chance of diagnosis due to the low number of eggs produced by the parasite. Therefore, serological methods can be useful for the purposes of diagnosis[11].

Ultrasound imaging (USG) may indicate common bile duct dilatation, intrahepatic bile duct dilatation, bile duct wall thickening, peripheral hypoechoic nodular lesions, flukes within the gallbladder, gallbladder wall thickening, and hepatomegaly[12]. The most important finding for the infection in biliary phase is, on the other hand, represented by small-sized linear filling defects in the distal choledocus as evidenced by endoscopic retrograde cholangiopancreatography (ERCP)[13,14].

If in acute phase, the infection is treated only with medication. *F. hepatica*-induced obstructions in the chronic phase of the infection may require ERCP[15]. ERCP allows for both the definitive diagnosis and treatment of the parasite[16,17].

The present study aimed to examine the demographic, radiological and laboratory characteristics of the *F. hepatica* infection and their effects on the differentiation of acute and chronic infections.

MATERIALS and METHODS

In this study, ethics committee approval was obtained from Diyarbakir Gazi Yasargil Training and Research Hospital dated 12/12/2018 and numbered 456. Patients diagnosed by extraction of *F. hepatica* parasite from the common bile duct with ERCP, ultrasonography suspected fasciola and diagnosed by ELISA *F. hepatica* IgG were included in the study. Cases without *F. hepatica* with ERCP, and those negative by ELISA or below the diagnostic value were not included into the study. Between January 2014 and December 2018, demographic data including age, sex, and place of residence (urban or rural area) and clinical findings at the time of presentation for patients diagnosed with *F. hepatica* were obtained retrospectively on the hospital data processing system. Laboratory data including *F. hepatica* serological testing, leucocyte, haemoglobin, haematocrit, platelet, eosinophil (rates over 5% and counts over 500 μ/L were considered to be high), urea, creatinine, sodium, potassium, AST ALT, GGT, ALP, total/direct bilirubin, amylase, lipase, CRP, and sedimentation level data were evaluated retrospectively. Whether *F. hepatica* was detected by ERCP procedure, ultrasonographic findings and whether they received treatment were retrospectively evaluated from the hospital data processing system.

With respect to the diagnosis of *F. hepatica* infection, the presence of characteristic findings (eosinophilia, and abnormal liver function tests) for *F. hepatica*[18,19] and/or a positive result in serological testing for *F. hepatica* were considered to indicate acute phase and the extraction of live *F. hepatica* in ERCP to point out to the chronic phase of the infection.

For the purposes of diagnostic testing for *F. hepatica*, DRG *F. hepatica* IgG ELISA (EIA-4503, DRG Instruments, Germany) kits were employed as the test that secures diagnosis in *F. hepatica*[21]. The DRG test decreases the diagnostic value due to cross-reaction in case of a second helminth infection[22]. The cut-off value for the kits was 11.5 DRG units (DU). *F. hepatica* IgG > 11.5 DU was considered positive.

Sphincterotomy and stone extraction were performed in all 7 patients who underwent ERCP.

All patients included into the study received triclabendazol (Egaten 250; Novartis, Switzerland) 250 mg tablet as a single dose of 10 mg/kg and the dose was repeated one month later.

Cases without the complete set of data were excluded from the study. Data not fully reaching

clinical, demographic and laboratory parameters were not evaluated.

Statistics Analysis

All statistical analyses were conducted on SPSS 22.0 Software (SPSS Inc., Chicago, IL, United States of America). The analysis of categorical data was performed on a X^2 test or Fisher's exact test and the median in Mann-Whitney U-test averages (interquartile range: 25-75) was employed for the analysis of non-parametric data. All patient characteristics were expressed in average + SD (minimum-maximum) or, when appropriate, in percentage. Statistical significance was identified as $p< 0.05$ in all tests.

RESULTS

A total of 17 patients were enrolled in the study including 1 (5.9%) male and 16 (94.1%) female patients (Table 1). The average age of the patients was 46.18 (min-max: 24-83) years (Table 2). The population included 10 (58.8%) acute and 7 (41.2%) chronic cases. The residential areas of the cases were divided between rural areas with 9 cases (52.9%) and urban areas with 8 cases (47.1%) (Table 1). The eosinophil count was higher than 5% in 10 (58.8%) cases and normal in others. The presenting diagnosis was *F. hepatica* in 13 (76.5%) cases; cholestatic enzyme elevation in 2 (11.8%) cases; pancreatitis in 1 (5.9%) case; and malignity in 1 (5.9%) case. The definitive diagnosis was secured with positivity result in serological *F. hepatica* IgG (58.8%) in addition to USG in 10 (59.1%) cases and with ERCP in 7 (41.2%) cases.

Ultrasonography determined 7 (40.9%) to be normal; 7 (40.9%) to have hypoechoic lesions; and 3 (17.5%) to present *F. hepatica* in the gallbladder.

A comparison between acute and chronic cases of *F. hepatica* indicated the average age to be median 45.5 (24-83) years to 46 (32-57) years ($p= 0.961$). Within the context of laboratory testing, there was no significant difference in terms of AST, ALT, GGT, ALP, bilirubin count, and CRP (Table 2) ($p> 0.05$). Albumin count

Table 1. Demographic and laboratory data for all patients

No	Age	Sex	Residence	Acute/chronic	FH IgG (DU)	Treatment	Eos (%)	Amylase (U/L)	Alb	Plt
1	34	F	Rural	Chronic	No data	ERCP + Tricl	7.4	94.00	3.8	166
2	45	F	Urban	Chronic	30	ERCP + Tricl	0.4	17.00	4.3	250
3	50	F	Rural	Chronic	10	ERCP + Tricl	14	-	4.2	306
4	57	F	Urban	Chronic	No data	ERCP + Tricl	17.6	2666.00	3.8	225
5	32	M	Rural	Chronic	No data	ERCP + Tricl	4.3	78.00	3.9	206
6	55	F	Urban	Chronic	No data	ERCP + Tricl	0.04	43.00	3.7	221
7	46	F	Urban	Chronic	15	ERCP + Tricl	9.1	86.00	4.3	201
8	51	F	Rural	Acute	40	Tricl	14.3	75.00	4.23	279
9	38	F	Rural	Acute	30	Tricl	60.8	45.00	4.5	278
10	41	F	Urban	Acute	22	Tricl	35.6	75.00	4.7	285
11	50	F	Rural	Acute	32	Tricl	6.4	120.00	4.8	349
12	24	F	Urban	Acute	18	Tricl	0.6	67.00	4.62	294
13	35	F	Urban	Acute	32	Tricl	7.2	60.00	4.62	308
14	53	F	Rural	Acute	30	Tricl	72.2	59.00	4.1	306
15	37	F	Rural	Acute	15	Tricl	0.7	107.00	4.6	332
16	54	F	Urban	Acute	17	Tricl	3.7	60.00	4.6	264
17	83	F	Rural	Acute	17	Tricl	1.2	66.00	3.9	339

FH: *Fasciola hepatica*, DU: DRG units, F: Female, M: Male, Alb: Albumin (g/dL), Eos: Eosinophil (%), Plt: Platelet ($x10^3/\mu L$), Tricl: Triclabendazol.

Table 2. Laboratory characteristics of patients

	Acute (n= 10) Median (25-75%)	Chronic (n= 7) Median (25-75%)	Total (n= 17) Mean (min-max)	p
Hb (g/dL)	13.15 (12.5-13-62)	13 (11.7-13.3)	12.76 (9.9-13.9)	0.433
Leucocytes (x10^3/μL)	10.12 (6.4-17.35)	5.6 (5.2-8.82)	10.13 (4.9-23.29)	0.51
Platelet (x10^3/μL)*	**300 (278.75-333.75)**	**221 (201-250)**	**271 (166-349)**	**0.004**
Eosinophil (x10^3/μL)	0.52 (0.14-5.2)	0.38 (0.03-0.51)	2.29 (0-16.45)	0.204
ALT (U/L)	30.5 (12.75-59.25)	50 (20-644)	110.41 (12-701)	0.305
AST (U/L)	23 (14.5-38.75)	27 (17-137)	61.64 (11-5537)	0.526
GGT (U/L)	27.5 (10.5-62.25)	84 (14-206)	79.94 (7-444)	0.118
ALP (U/L)	95 (66-215)	107 (76-179)	125.58 (45-266)	0.591
Total bilirubin (mg/dL)	0.3 (0.26-0.71)	0.37 (0.233-3.9)	1.01 (0.13-6.28)	0.524
Sedimentation (mm/hour)	30 (15.5-41.5)	17 (11.5-38.25)	28.15 (11-60)	0.315
CRP (mg/L)	3.27 (2.92-6.5)	7.5 (2.57-35)	17.66 (0.14-149)	0.328
Amylase (U/L)	66 (69.5-91)	82 (51.75-2021)	255 (17-2666)	0.379
Albumin*	**4.6 (4.19-4.64)**	**3.9 (3.8-4.3)**	**4.27 (3.7-4.8)**	**0.009**

* Statistically significant items are indicated by the superscript ($p< 0.05$).

was 4.6 g/dL to 3.9 g/dL (p= 0.009) and platelet count 300 x 10^3/μL to 221 x 10^3/μL (p= 0.004) for acute and chronic cases, respectively, and these results were statistically significant.

Chronic cases had been treated with ERCP + 10 mg/kg triclabendazol, while acute cases had been managed only with triclabendazol at 10 mg/kg (Table 1).

The laboratory data pertaining to the cases were as specified in Table 2.

DISCUSSION

F. hepatica infection is observed endemically among people in certain geographical regions. Its prevalence was identified to range from very low to very high[23]. In recent years, this infection has been seen to occur commonly among individuals along with climatic and global changes. In addition, the infection is considered to be increasingly significant by reason of its elevated pathogenicity in acute and advanced chronic phases in the endemic regions of developing countries[24].

F. hepatica infection may be divided in clinical and laboratory terms into two different periods, namely the acute phase involving hepatic parenchyma to a greater extent and the chronic phase affecting the biliary system[25].

Although DRG *F. hepatica* IgG ELISA test is sensitive and specific up to 100%, its sensitivity decreases in a second helminthic infection[20,21]. If this possibility is available, the history of the patients should be questioned (watercress or fresh green vegetables or living in the hyperendemic region, etc.) and the diagnosis should be confirmed by a second serological test[22]. In this respect, we strengthened the accuracy of the diagnosis.

The percentage of female cases has been identified to be 88.2% by Akpinar et al.[26]and 86.3% by Kaya et al.[27]. Similarly, cases in the present study were females.

History of ingesting watercress and the presence of eosinophils increase the probability of *F. hepatica* infection[28]. The presence of eosinophils has been found at 79% by Ulger et al.[29] and 82% by Akpinar et al.[26]. The present study identified the percentage of eosinophils to be lower. We did not determine the occurrence of eosinophils in our region at percentages as high as those reported in the literature.

Review of the residential information pertaining to the cases indicated in a study concerning 17 chronic cases of *F. hepatica* infection has found 10 cases to be residing in urban areas and

7 in rural locations[26]. The breakdown of the cases in the present study by residential location is consistent with the related literature.

Imaging methods are of great significance for the diagnosis of *F. hepatica* infections. Transabdominal ultrasound imaging may indicate lesions in the biliary tract although not as a finding specific to *F. hepatica* infection[19]. In a study of 7 cases by Sezgin et al., 3 (42.8%) had normal ultrasonographic findings, common bile duct dilatation in 1 (14.2%) case, dilated common bile duct filled with isoechoic tissue with liver tissue in 1 (14.2%) case, echogenicity in gallbladder in 1 (14.2%) case, and 1 (14%) 2) polyps were detected in the gallbladder[30]. Similarly, the present study found normal USG, hypoechoic lesions and *F. hepatica* in the gallbladder. Ultrasound findings offer a method that may assist in the diagnosis as complementary elements for other findings rather than provide for definitive diagnosis.

F. hepatica located in the biliary tracts in the chronic phase may be evident with the manifestation of biliary colic, jaundice or cholangitis. Certain patients had also been diagnosed upon pancreatitis[7]. Kaya et al. identified acute pancreatitis in 3 (37.5%) out of 8 cases of *F. hepatica* infection[13].

A comparison between acute and chronic cases of *F. hepatica* infection indicated cholestatic enzyme levels including AST, ALT, GGT, ALP, and bilirubin and CRP values, but such differences were not statistically significant ($p> 0.05$) (Table 2).

Hypoalbuminemia can be seen as a result of the combined effects of inflammation, inadequate protein and caloric intake in patients with chronic disease. Inflammation and malnutrition reduce the concentration of albumin by reducing the rate of synthesis. Inflammation alone leads to a greater fractional catabolic rate and more albumin out of the vascular compartment when inflammation is excessive. A vicious cycle occurs in which inflammation creates anorexia, decreases the effective use of dietary protein and energy intake, and increases catabolism of important somatic protein and albumin. Inflammation is associated with vascular diseases and possibly causes damage to the vascular endothelium and may cause hypoalbuminemia[31]. In our study, albumin levels in acute and chronic cases were 4.6 g/dL and 3.9 g/dL ($p= 0.009$), respectively (Table 2), and were significantly lower in chronic cases. Prospective studies need to be conducted with the inclusion of a larger sample of cases to explain the relatively low albumin in chronic *F. hepatica*.

Platelet production can be reduced by low levels of thrombopoietin (TPO) and direct bone marrow suppression. Hepatic production of TPO plays an important role in thrombopoiesis. TPO regulates platelet production and maturation[32]. TPO is performed by both parenchymal cells and sinusoidal endothelial cells in the liver and released into the circulation at a constant rate[33]. In cases such as drugs, viruses, autoimmune diseases, cirrhosis, etc. hepatic TPO production is affected and platelet count decreases[34]. In our study, platelet count was 300 x 10^3/µL and 221 x 10^3/300 L ($p= 0.004$) in acute and chronic *F. hepatica* cases, respectively, and significantly lower in chronic cases. In chronic *F. hepatica* cases, we think that the lower platelet count is due to decreased hepatic TPO production. Prospective studies need to be conducted with the inclusion of a larger sample of cases to explain the relatively low platelet counts in chronic *F. hepatica*.

Our study limitation: Diagnosis of *F. hepatica* infection, presence of characteristic findings (abdominal pain, fever, eosinophilia, and abnormal liver function tests), serological tests for *F. hepatica* are considered as acute phase[18,19]. In our study, lack of history and clinical findings was an important deficiency in the diagnosis of fascioliasis.

CONCLUSION

The female sex and presence of eosinophils constitute findings that raise suspicion for infection with *F. hepatica*. Laboratory data alone do not appear to assist the differentiation between acute and chronic cases to a great extent, evaluation with detailed history and clinical findings may help in this distinction. Albumin and platelet counts are lower among chronic cases. This fact points out to a need for prospective studies incorporating a larger sample of cases.

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CONFLICT of INTEREST

There is no conflict of interest for any author.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: NT

Analysis/Interpretation: NT

Data Acquisition: NT

Writting: NT

Critical Revision: NT

Final Approval: NT

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