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Infantile cholestatic liver diseases: retrospective analysis of 190 cases

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Summary

Aim: The aim of the study was to evaluate the patients between 0 and 2 years of age who were followed up with a diagnosis of cholestatic liver disease.

Material and Method: 190 patients (84 girls, 106 boys; median age, 3 months) with cholestatic liver disease who were followed up in our clinic between 2004 and 2011 were evaluated retrospectively. Clinical, laboratory, imaging and histopathological findings, prognosis and response to therapy were assessed. The patients were divided into two groups as hepatocellular and canalicular cholestasis and the association between clinical and laboratory findings was evaluated.

Results: The causes of cholestasis included progressive intrahepatic familial cholestasis (n=38), extrahepatic biliary system disorders (n=32), total parenteral nutrition and sepsis associated cholestasis (n=19), genetic disorders (n=18), metabolic diseases (n=16), syndromic and non-syndromic ductopenia (n=14), idiopathic neonatal hepatitis (n=11) and others (n=15). The cause of cholestasis was not determined in 27 patients. A positive correlation was found between canalicular cholestasis and presence of acholic stool ($p<0.0001$) and elevated gamma glutamyl transferase ($p=0.001$) and a positive correlation was found between hepatocellular cholestasis and presence of systemic symptoms ($p=0.018$) and consanguinity ($p=0.001$). Histopathology was found to be the most valuable diagnostic method for biliary atresia.

Conclusions: In our series, extrahepatic biliary system disorders, familial, genetic and metabolic diseases were the most important causes of cholestasis. A strong association was found between canalicular cholestasis and presence of acholic stool and elevated gamma glutamyl transferase and a strong association was found between hepatocellular cholestasis and consanguinity and systemic symptoms. *(Turk Arch Ped 2012; 47: 165-171)*

Key words: Cholestasis, jaundice

Introduction

Cholestasis is a clinical condition characterized by a decrease in bile formation and bile flow and accumulation of substances which are expected to be excreted in bile (1,2). Clinically it is associated with findings including jaundice, pruritus and acholic stools and is differentiated with direct bilirubinemia (1,3). In newborns, the frequency of cholestatic liver disase ranges between 1/2500 and 1/5000 (4). Cholestasis is an important finding of hepatobiliary diseases in different age groups, however, it is observed more frequently in the newborn and early infancy period. The reason for this is that the systems providing bile production or bile flow are immature or more sensitive compared to older age groups (1). Cholestatic liver diseases are divided into two groups as obstructive (canalicular) and hepatocellular diseases. Biliary atresia constitutes the most important proportion of obstructive liver diseases (5). The main hepatocellular causes of cholestasis include infections, genetic-metabolic diseases and toxic causes. However, regional or ethnic differences may be observed in the distribution of the causes (6,7,8,9,10). Cholestatic liver disease can present as acute hepatic failure, transient cholestasis or chronic liver disease in infancy. In an important proportion of the patients, early diagnosis and treatment can stop the clinical course which may be destructive or progressive (3).

In this study, 190 patients between 0 and 2 years of age who were followed up in our clinic between 2004 and 2011 with a diagnosis of cholestatic liver disease were examined retrospectively.

Material and Method

190 patients with a diagnosis of cholestatic liver disease who were followed up in our hospital between 2004 and 2011 were

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examined retrospectively. Demographic properties, complaints, the age of onset of complaints, presence of acholic stools, birth ages and weights, consanguinity between the mother and the father, presence of familial history of a similar disease and physicial examination findings of the patients were obtained from patient files and recorded. Hepatic function tests, triglyceride, cholesterol levels, complete blood count, infection markers and metabolic and genetic tests were evaluated in terms of cholestasis. Diagnostic imaging methods (ultrasonography, scintigraphy, magnetic resonance cholangiography) and histopathologic examinations were evaluated. After these evaluations the cases were divided into two groups as hepatocellular and canalicular causes. While extrahepatic biliar system diseases (biliary atresia, choledoc cyst etc.) and intrahepatic ductopenias (syndromic and non-syndromic) constituted the canalicular causes, familial cholestases, metabolic and genetic diseases, infections, toxic causes, endocrinopathies and idiopathic neonatal hepatitis constituted hepatocellular causes (Table 1).

The patients were evaluated in terms of disorders of absorption of fat and fat-soluble vitamins and problems related to accumulation of substances excreted in bile (pruritus, xantomatosis) which are the short-term and long-term complications of cholestatic liver disease and in terms of complications of end-stage liver disease.

Clinical follow-up times, surgical treatments performed during follow-up and mortality rates were evaluated.

SPSS 17.0 program was used for statistical analysis. Student's t test was used for variables which showed normal distribution and Mann-Whitney U test was used for variables which did not show normal distribution. Chi-square test was used for non-continuous variables. Spearman's correlation test was used to evaluate the relation between clinical and laboratory variables and the type of cholestasis (hepatocellular or canalicular). Variables with a p value below 0.05 in Spearman's correlation test were examined using multivariate analysis with backward stepwise logistic regression. A p value of <0.05 was considered to be significant in statistical analyses used.

Results

The ages of the patients ranged between one day and 24 months (median age: 3 months). 84 of the patients were female and 106 were male. Complaints reported at presentation included jaundice (64.7%), intermittent acholic stools (34.7%), vomiting (16.8%), low weight gain (15.8%), diarrhea (14.7%), prutitus (13.7%), abdominal swelling (9.5%), bleeding (8.9%) (mucosal and intracranial), growth retardation (5.8%), seizure (4.2%), inattentiveness (4.2%), restlessness (3.7%), cough (3.7%), developmental delay (3.2%), frequent infections (2.1%), swelling in the eyelids (2.1%) and rash. 27 patients (14.2%) were diagnosed as cholestasis when they were referred to a physician for other causes.

While approximately ¼ of the patients were premature and/or low birth weight infants, ¼ had been followed up in the intensive care unit during the newborn period. Consanguinity between the mother and the father was found in 85 of the patients (44.5%), history of death of a sibling was found in 31 (16.2%) patients and familial history of a similar disease was found in 19 patients (10%).

On physical examination, jaundice (64.7%), hepatomegaly (56.3%), splenomegaly (42.6%), continuous acholic stools (19.3%), cardiac murmur (7.3%), ascites (6.8%), abnormal lung

Table 1. Causes of cholestasis

CANALICULAR CAUSES	n (%)
Extrahepatic biliary system diseases	**32 (16.8)**
Biliary atresia	24
Choledoc cyst	5
Viscous bile sydrome	2
Bile mud	1
Ductopenias	**14 (7.4)**
Syndromic (Alagille syndrome)	8
Non-syndromic	6
HEPATOCELLULAR CAUSES	
Familial cholestases	**38 (20)**
Progressive, familial intrahepatic cholestasis	34
Benign recurrent intrahepatic cholestasis	4
TPF-Sepsis related cholestasis	**19 (10)**
Genetic cholestases	**18 (9.5)**
Cystic fibrosis	10
Alpha-1 antitrypsin deficiency	7
46 XX del (13) t (4:13) (q25:p13) trisomy 4q25-qter	1
Metabolic diseases	**16 (8.4)**
Galactosemia	8
Niemann-Pick type C	4
Disorders of fructose metabolism	2
Congenital glycosylation defect	1
Mitochondrial cytopathy	1
Idiopatic neonatal hepatitis	**11 (5.8)**
Transient cholestasis	**8 (4.2)**
Infections	**5 (2.6)**
Sepsis	2
Congenital CMV infection	2
Urinary tract infection	1
Endocrine causes	**1**
Pituiter failure	1
Autoimmune diseases	**1**
Coombs (+) hemolytic anemia-giant cell hepatitis	1
Unknown cause	**27 (14.2)**
Total	**190**

sounds (6.3%), pretibial or periorbital edema (5.2%), mental motor retardation (5.2%), venous collaterals (4.7%), hypotonia (4.7%), dysmorphic findings (3.7%), cataract (1.6%) and finger clubbing (1%) were found.

Examinations revelaed the following etiologies of cholestasis: a) canalicular causes: extrahepatic biliary system problems (n=32), syndromic and non-syndromic ductopenias (n=14), b) hepatocellular causes: familial cholestases (n=38), total parenteral nutrition and sepsis associated (n=19), genetic diseases (n=18), metabolic diseases (n=16), idiopathic neonatal hepatitis (n=11), transient cholestasis (n=8), infections (n=5), endocrine causes (n=1) and autoimmune problems (n=1). The etiology of cholestasis could not be determined in 27 patients (Table 1).

When the clinical poperties of the patients were evaluated by the type of cholestasis, it was observed that male patients were found with a higher rate in the group with hepatocellular cholestasis compared to the group with canalicular cholestasis ($p>0.05$). However, the difference was not statistically significant. Consanguinity, history of death of a sibling, history of a similar disease and systemic findings were found with a higher rate in patients with hepatocellular cholestasis compared to patients with canalicular cholestasis ($p<0.05$). History of acholic stools was found with a significantly higher rate in patients with canalicular cholestasis ($p<0.001$) (Table 2).

When the patients were evaluated according to laboratory findings, AST, ALT, GGT, bilirubin, triglyceride and cholesterol values were found to be significantly higher in patients with canalicular cholestasis compared to patients with hepatocellular cholestasis ($p<0.05$). On the other hand, PT and INR values in patients with hepatocellular cholestasis were found to be significantly higher compared to patients with canalicular cholestasis ($p<0.05$) (Table 2).

When potential clinical and laboratory findings which are thought to be related to the type of cholestasis were examined with Spearman's correlation test, no significant relation was found between acholic stools, systemic symptoms, history of consangiunity and similar disease, GGT, direct bilirubinemia, AST and the type of cholestasis. The combined effect of these variables was examined using multivariate backward stepwise regression test. Accordingly, a positive relation was found between the diagnosis of canalicular cholestasis ($p<0.0001$) and

Table 2. Distribution of clinical and laboratory findings in patients with canalicular and hepatocellular cholestasis

	Canalicular cholestasis	Hepatocellular cholestasis	p
Male gender, %	21 (45.7)	86 (59.7)	0.094
Persistent acholic stools, %	28 (65.1)	21 (14.8)	**<0.001**
Systemic findings, %	10 (23.8)	77 (54.6)	**<0.001**
Birth weight < 2500 g, %	14 (37.8)	49 (39.2)	0.881
Consanguinity, %	11 (28.6)	72 (52.2)	**0.004**
History of death of a sibling, %	1 (2.4)	30 (22.1)	**0.006**
History of a similar disease, %	1 (2.4)	26 (19.1)	**0.006**
Hepatomegaly, %	28 (66.7)	79 (57.2)	0.276
Splenomegaly, %	16 (38.1)	65 (47.1)	0.304
AST, IU/L*	198 (119-260)	129 (76-234)	**0.037**
ALT, IU/L*	119 (66-173)	85 (48-138)	**0.043**
ALP, IU/L*	640 (413-978)	565 (345-849)	0.090
GGT, IU/L*	443 (131-1043)	137 (51-289)	**0.00001**
T bilirubin, mg/dL*	8.6 (5.6-12)	4.8 (1.0-10)	**0.002**
D bilirubin, mg/dL*	6 (3.6-8.8)	3.0 (0.5-6)	**0.00015**
Albumin, g/dL*	3.9 (33.8-43)	3.8 (32-43)	0.81
Triglyceride, mg/dL*	163 (121-240)	126 (87-192)	**0.033**
Cholesterol, mg/dL*	155 (137-255)	135 (105-177)	**0.007**
PT, sec*	12.4 (11.4-14)	13.3 (12.0-17)	**0.024**
INR*	1.0 (0.97-1.2)	1.1 (1.0-1.4)	**0.016**
Fibrinogen, mg/dL*	192 (167-236)	179 (116-232)	0.17
Hb, g/dL*	10.2 (9-11.4)	10.3 (9.1-12)	0.48
Leucocytes, x109/L*	11.6 (9.4-15.5)	10.8 (8.1-13.9)	0.09
Platelets, x109/L*	390 (286-477)	307 (224-421)	**0.037**

*Values are given as median (25^{th} and 75^{th} percentages).

Table 3. Evaluation of the combined effect of possible clinical and laboratory findings which are thought to be related to the the type of cholestasis according to multivariata backward stepwise regression test.

Variables	Beta	Odds ratio	Confidence interval (±% 95)	p
Presence of acholic stools	2.869	17.611	5.821-53.288	<0.0001
Presence of systemic symptoms	-1.323	0.266	0.089-0.793	0.018
Consanguinity	-1.976	0.139	0.043-0.449	0.001
GGT (>600 IU/L)	2.293	9.901	2.685-36.511	0.001

Table 4. Liver biopsy findings of the patients

Histopathologic findings	n	%
Microanatomy		
Normal	75	61.5
Pre-cirhhotic	20	16.4
Cirrhotic	27	22.1
Fibrosis		
None	10	8.2
Mild	43	35.2
Moderate	26	21.3
Severe	43	35.2
Storage		
None	106	86.9
Micro-macrovesicular steatosis	6	4.9
Macrovesicular steatosis	6	4.9
Alpha-1 antitrypsin granules	3	2.5
Lipid storage cell	1	0.8

increased GGT (p=0.001) and between the diagnosis of hepatocellular cholestasis and presence of systemic symptoms (p=0.018) and consanguinity (p=0.001) (Table 3).

In all patients, the liver and bile ducts were evaluated by ultrasonography. Contracted gallbaldder was found in 38 patients, increased echogenicity in the liver was found in 27 patients, heterogeneous liver paranchima was found in 17 patients, ascites was found in 11 patients and bile mud was found in three patients. Specific findings of biliary atresia were found in 15 patients: dilatation in intrahepatic or extrahepatic bile ducts was found in 5 patients, the gallbladder could not be visualized in four patients, choledoc cyst was found in 3 patients and triangular cord sign was found in two patients. In one patient in whom the gallbladder could not be visualized, dilatation in intrahepatic bile ducts was observed.

Echocardioagraphy was performed in 70 patients in whom cardiac murmur was heard on physical examination or who were thought to have cardiac anomalies in addition to cholestasis. Atrial defect was found in 29 of these patients, patent foramen ovale was found in 11 patients, peripheral pulmonary stenosis was found in 11, valvular pulmonary stenosis was found in 4 patients, ventricular septal defect was found in 5 patients, patent ductus arteriosus was found in 5 patients, aortic stenosis was found 2 patients, aortic coartation was found in one patient and double outlet right ventricle was found in one patient. More than one cardiac anomaly was found in 23 patients.

It was reported that radioactive material was not delivered into the intestines in 22 of 42 patients in whom scintigraphic examination was performed. A diagnosis of choledoc cyst was made in 4 patients using magnetic resonance cholangiography. Findings compatible with choledoc cyst were found on ultrasonography only in 2 of 4 patients in whom a diagnosis of choledoc cyst was made on magnetic resonance cholangiography.

Liver biopsy was performed in 122 (63.9%) patients. Biopsy was performed for three times in 2 patients and 2 times in 19 patients. Histopathology revealed cirrhosis in 27 patients and precirrhotic characteristics in 20 patients. The microanatomy of the liver was preserved in 75 patients. While mild fibrosis was observed in 43 patients, moderate fibrosis was observed in 26 patients and severe fibrosis was observed in 6 patients. No fibrosis was found in 10 patients. Micro ve macrovesicular steatosis was found in 6 patients, only macrovesicular steatosis was found in 6 patients, alpha-1-antitrypsin granules were found in 3 patients and lipid storage cells were found in one patient (Table 4).

For the diagnosis of biliary atresia which is important in terms of early diagnosis among the causes of canalicular cholestasis the sensitivity, specificity and negative and positive predictive values for acholic stools, increased GGT, biliary scintigraphy, ultrasonography and biopsy findings were calculated (Table 5). In the diagnosis of biliary atresia, histopathology is the most sensitive test and presence of acholic stoools was found to have a sensitivity similar to scintigraphy. Specific findings for biliary atresia including triangular cord sign on ultrasonography, cystic formation and inability to visualize the gallbladder were found to be the most specific tests for biliary atresia similar to histopathology. Acholic stools, a GGT value above 600 U/L, ultrasonography and histopathology had a negative predictive value of >90% (Table 5).

When an evaluation was made in terms of complications of cholestasis, portal hypertension was found in 39 patients using Doppler ultrasonography and/or endoscopic examinations. Esophageal varice and/or portal gastropathy was found in 28 of 43 patients in whom endoscopic examination was performed considering development of portal hypertension because of marked splenomegaly.

When an evaluation was made in terms of fat-soluble vitamin deficiencies, vitamin D deficiency was found in 43 patients (58.1%), vitamin A deficiency was found in 8 patients (29.6%)

Table 5. Sensitivity, specificity and negative and positive predictive values of the variables in the diagnosis of biliary atresia				
	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Acholic stools	83	74	96	37
GGT>600 U/L	57	92	92	57
Positive scintigraphy	81	65	85	59
Findings specific for	57	98	92	87
Biopsy	85	96	96	85

US: Ultrasonography, NPV: negative predictive value, PPV: positive predictive value

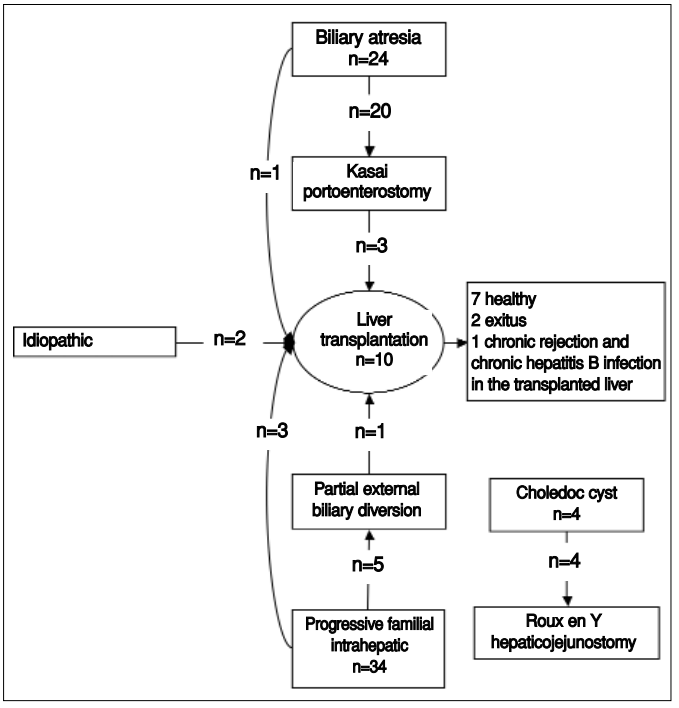

Figure 1. Surgical operation performed in the patients

and vitamin E deficiency was found in 6 patients (22.2%). In 38 patients (17.3%), prothrombin time was found to be longer compared to the normal value by age. A negative relation was found between vitamin D level and serum alkaline phosphatase level ($r = -0.258$, $p = 0.028$).

Fat-soluble vitamin support and ursodeoxycholic acid were given to all patients with a diagnosis of cholestasis. Special diet, enzyme support, antibiotic and hormone support were added in patients with specific diagnoses. Surgical treatment was required in 38 patients. Kasai portoenterostomy was performed in 20 patients who were diagnosed as biliary atresia, Roux en Y hepaticojejunostomy was performed in 4 patients who were diagnosed as choledoc cyst, partial external biliary diversion was performed in 5 patients who were diagnosed as familial cholestasis and liver transplantation was performed in 10 patients (Figure 1).

The patients were followed up with a period ranging from one month to 224 months (median: 11 months). Cholestatic liver disease was completely recovered with supportive or specific treatments in 63 (33.2%) of the patients. While problems related to the primary disease continued in 37 patients (19.5%), cholestatic findings regressed. 14 patients (7.4%) are being followed up with the findings of active cholestasis and 13 patients (6.8%) are being followed up with the findings of end-stage liver disease. While 13 patients (6.8%) never attended follow-up visits after the diagnosis, 33 patients (7.4%) did not attend follow-up visits regularly. 9 of the patients who did not attend follow-up visits regularly had end-stage liver disease. 17 patients (8.9%) were lost due to liver failure and/or complications of liver failure. 7 of 10 patients who were undegone liver transplantation are still being followed up in a healthy state, whereas 2 patients were lost in the early post-operative period. Chronic rejection and chronic hepatitis B infection were observed in one patient.

Discussion

In the newborn and infancy period, the mechanisms of production and excretion of bile are more sensitive to both liver diseases and systemic diseases. Therefore, cholestasis may be observed as a finding of different diseases. The causes of cholestasis include extrahepatic biliary diseases including biliary atresia, choledoc cyst, gallbladder mud and viscous bile syndrome and intrahepatic cholestatic diseases including familial cholestasis, syndromic and non-seyndromic paucity of the bile ducts, metabolic diseases, genetic diseases and infections (11). When the distribution of the diseases causing cholestasis in our series was evaluated, it was observed that extrahepatic biliary system diseases, familial, genetic and metabolic diseases predominated in the etiology. The high rate of consanguineous marriages in our country may explain this distribution. In previous series reported in our country, the main causes of cholestasis were found to be biliary atresia, idiopathic neonatal hepatitis and cytomegalovirus (CMV) infection (9,10,12,13,14). In recent years, a decrease in the number of idiopathic cases and an increase in the number of genetic and metabolic causes has been observed in the series reported in our country (10,14). This change in the eitologic distribution may be explained by an increase in specific diagnoses with the advances in diagnostic examinations and

by the fact that our center is a reference center for genetic and metabolic diseases.

In cases of neonatal cholestasis, specific diagnoses are attempted to be reached with a combination of clinical, laboratory, radiologic and histopathologic findings (11). As in our series, acholic stools, organomegaly and disorders in the liver function tests constitute important clinical and laboratory findings, but none of the data used in diagnosis reaches adequate sensitivity and specificity by itself (15). In the diagnostic approach, the first step is differentiation of extrahepatic causes and intrahepatic causes which are different in terms of physiopathology and treatment (16). Although presence of acholic stools is the main finding of biliary atresia, it may also be observed in patients with severe intrahepatic cholestasis (3,17). Infants with intrahepatic cholestasis generally have an ill-looking appearance carrying the signs of different systemic diseases, congenital infections or some syndromes (18,19,20). In our series, the presence of acholic stools supported extrahepatic biliary system disease and presence of systemic symptoms supported intrahepatic cholestasis. In our study, the presence of acholic stools was found to be considerably valuable with a sensitivity of 90% and a negative predictive value of 95% (21,22). Therefore, it was thought that delay in the diagnosis of biliary atresia could be prevented by using stool color charts in screening of biliary atresia in our country.

There is no biochemical test or imaging method alone or a combination of these to adequately differentiate extrahepatic diseases and intrahepatic diseases. Clinical and laboratory findings in 10% of the patients with intrahepatic cholestasis are similar to the ones found in patients with estrahepatic causes (16). However, it has been reported that increased GGT together with an alkaline phosphatas value of >600U/L is valuable in terms of extrahepatic biliary disease and aminotransferase levels above 800 U/L are valuable in terms of hepatocellular disease (23). It should be kept in mind that very high ALP and GGT levels can also be observed in ductopenias and alpha-1 antitrypsin deficiency (23). In our study, a relation between extrahepatic biliary disease and GGT was found in the multivariate regression test, but no significant relation was found with ALP values. In our study, an inverse relation was found between vitamin D levels and ALP. Since rahitis is a common complication observed in patients with cholestasis, ALP values should be evaluated carefully.

Imaging methods are important in the diagnosis of extrahepatic biliary system diseases. Findings including choledoc cyst, bile mud, dilatations in the biliary ducts, triangular cord sign, inability to visualize the gallbladder, situs abnormalities and polysplenia suggest extrahepatic biliary system diseases (17,24). In our study, it was observed that the sensitivity of specific findings including inability to visualize the gallbladder, triangular cord sign and presence of a cyst was high. However, the fact that the procedure is dependent on the individual and the problem of compliance of infants seem to be limiting factors. Hepatobiliary scintigraphic examinations can be used in the diagnosis of extrahepatic biliary system diseases. The sensitivity of scintigraphy for excluding extrahepatic biliary system diseases reaches up to 100% (11). However, it is being used with a gradually lower rate in the diagnosis because it has low specificity, is a time-consuming method and delays surgery (22). Because of these factors scintigraphy is not a commonly used method in our clinic either. Our results suggest that hepatobiliary scintigraphy has no additional diagnostic benefit in patients with presence of acholic stools.

Liver biopsy can be considered as the most beneficial method for differential diagnosis in patients with cholestasis. With an experienced pathologist and clinical compatibility it can give a spesific diagnosis and its sensitivity reaches 100% and its specificity reaches 80% in the diagnosis of extrahepatic obstructive pathologies (21,22,25). Findings including increase in intralobular bile ducts, bile plugs, edema and fibrosis in the portal area support biliary atresia (26). In our study, biopsy was found to have a specificity of 85% and a sensitivity of 96% in the diagnosis of biliary atresia. In the study performed by Lai et al. (21) in which approach to the infant with cholestasis was evaluated, liver biopsy was found to be the most accurate test in the diagnosis of biliary atresia. In the same study, hepatic histopathology, color of the duodenal fluid, abdominal ultrasonography and stool color were found to be the most valuable tests in the multivariate logistic regression test (21). In recent years, great advances have been made in genetic tests. Use of these tests in investigation of patients with cholestasis may decrease the need for other laboratory tests. However, traditional dignostic methods are valid for the present time, since genetic tests are expensive, can not be performed in all centers and no genetic test is available for some diseases including biliary atresia.

Determination of treatable causes in infants with cholestasis and starting of the appropriate treatment may prevent liver demage and saves time for liver transplantation by slowing down the course of the disease (3,20). In cholestasis of infancy, chronic liver disease and cirrhosis can be prevented by early diagnosis and treatment of extrahepatic biliary system diseases including mainly biliary atresia and causes of intrahepatic cholestasis including infections, metabolic diseases, endocrine diseases and familial cholestasis (3). Even if specific diagnoses are not reached in infants with cholestasis, important complications including intracranial bleeding, osteoporosis and malnutrition due to deficiencies of fat-soluble vitamins can be prevented by starting supportive treatment methods as soon as possible (3). Considering that 6 patients in our series were diagnosed after intracranial bleeding occured the importance of administration of vitamin K in patients with cholestasis by the first physician who examines the patient is manifested.

Liver transplantation is the only option in treatment of infants with cholestasis with no specific treatment and with end-stage liver disease (27). Cholestasis in infancy constitute more than half of the causes of liver transplantation in children (27,28,29).

Considering lost cases because of end-stage liver disease and the possibility that a proportion of the patients who did not attend follow-up visits regularly might have been lost it was concluded that liver transplantation was not performed efficiently enough as a treatment option in this age group.

In the newborn period, cholestatic liver disease should be considered in presence of jaundice lasting longer than 14 days. Patients in whom cholestasis is considered should be referred to centers which have a pediatric hepatology division for early diagnosis and treatment after administration of vitamin K. In our series, extrahepatic biliary diseases, genetic and metabolic diseases were predominant in the etiology of cholestasis. The high rate of consangineous marriages may explain this distribution. In our series, a strong relation was found between canalicular diseases and the presence of acholic stools and increased GGT and between hepatocellular diseases and consangineous marriages and presence of systemic findings. With these findings it was thought that use of stool charts for screening of biliary atresia would also be valuable in early diagnosis in our country. Cholestasis regressed in an important proportion of the patients who attended follow-up visits. It was concluded that liver transplantation is not being performed efficiently enough as a treatment option in this age group considering lost cases because of end-stage liver disease and the possibility that a proportion of the patients who did not attend follow-up visits regularly might have been lost.

Conflict of interest: None declared.

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