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Liver Cirrhosis and Portal Hypertension in Cystic Fibrosis

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SUMMARY

Introduction As the expected survival improves in individuals with the cystic fibrosis (CF), so they may be faced with a number of medical complications.

Objective The aim of this study was to analyze the prevalence of liver cirrhosis in our CF population as well as the clinical and genetic characteristics of these patients.

Methods All patients older than 2 years (n=96) were screened for liver disease. Liver cirrhosis was defined by ultrasonographic findings of distinct heterogeneity of liver parenchyma and nodular liver surface and/or by liver biopsy findings. Enlarged spleen, distended portal vein and abnormal portal venous flow indicated portal hypertension. Clinical and genotype data were analyzed.

Results Sixteen patients were found to have liver cirrhosis, three of them with portal hypertension. All patients had pancreatic insufficiency. Nutritional status expressed as standard deviation score (Z score) for weight, height, and body mass index was as follows: zW=-0.40±1.24, zH=-0.83±1.02, and BMI=20.1±2.3. CF patients with liver cirrhosis generally had mild-to-moderate lung disease, with average FVC and FEV_1 values of 97.1±16.5% of predicted and 87.9±23.5% of predicted, respectively. Genetic analysis showed high frequency of F508del mutation in the group with cirrhosis (90.6%).

Conclusion The prevalence of liver cirrhosis in our CF population older than 2 years was 16.6%. Patients with pancreatic insufficiency and severe CFTR mutations, especially F508del, were exposed to higher risk of developing liver cirrhosis. Liver cirrhosis has no significant impact on the pulmonary function and the nutritional status, until the end-stage liver disease.

Keywords: cystic fibrosis; CFTR gene; liver cirrhosis; portal hypertension

INTRODUCTION

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease of the Caucasian population, with an incidence of approximately 1 in every 3000 live births worldwide. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This results in dysfunction of the apical membrane CFTR protein in epithelial cells on mucosal surfaces, which functions principally as a cAMP induced chloride channel and appears to be capable of regulating other ion channels [1, 2]. Mutations in the CFTR gene cause inspissated secretions leading to disease of the affected organs [3]. Since the CFTR gene was cloned in 1989 [4], over 1800 mutations of this gene have been identified [5]. The most common mutant allele is the F508del, which is responsible for approximately two-thirds (66%) of all CF chromosomes worldwide. However, there is a great mutational heterogeneity in the remaining one-third of all alleles [6]. The phenotypic expression of CF is extremely heterogeneous in terms of severity and type of organs involved: while the sweat glands, lungs, pancreas and Wolffian ducts in male subjects are affected in the majority of patients, the liver and intestines are less frequently involved.

Although liver cirrhosis was recognized as a complication of CF in Anderson's original description in 1938, the importance of subclinical liver disease has been eclipsed by more obvious respiratory and pancreatic signs and symptoms. More effective management of these has resulted in highly improved survival, and so liver disease has become important to a large number of CF patients and those involved in their care. A spectrum of hepatobiliary manifestations observed in CF patients, from mainly asymptomatic elevation of serum liver enzymes, neonatal cholestasis and hepatic steatosis to multilobular cirrhosis and gallbladder abnormalities and approximate frequency of these manifestations were shown in Table 1 [7, 8].

The pathogenesis of CF-associated liver disease is considered to be secondary effect of the underlying defect. The CFTR gene in the normal human liver is expressed in the epithelia of the intrahepatic and extrahepatic bile ducts and gallbladder, and is not expressed in hepatocytes or other cells of the liver [9]. CFTR seems to contribute to normal bile formation and alkalization through the regulation of Cl, HCO_3 and water transport.

The progression from cholestasis (decreased bile flow) to focal biliary cirrhosis and to multilobular cirrhosis takes years in some CF patients, or never occurs in other CF patients. The development of fibrotic liver lesion is usually clinically silent. Many patients with cirrhosis caused by CF are well compensated and completely asymptomatic and may even have normal liver blood tests. However, with progression of the fibrotic liver lesion, these patients are prone to decompensate and develop symptoms of portal hypertension, rarely liver failure, requiring liver transplantation. What

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Table 1. Hepatobiliary manifestations of cystic fibrosis

Condition	Frequency (%)
Asymptomatic elevation of serum liver enzymes	10-46
Neonatal cholestasis	2
Hepatic steatosis	20-60
Hepatomegaly	30
Focal biliary cirrhosis	10-72
Multilobular cirrhosis	7-20
Cholelithiasis	1-10
Micro gallbladder	20-30
Common bile duct stenosis	<2

Table 2. A grading scheme for liver parenchymal appearances in cystic fibrosis on ultrasonography

Grade	Appearance
N	Normal
I	Increased liver echogenicity
II	Slight subjective coarsening of liver echo texture
III	Definite coarsening, no nodularity
IV	Parenchymal distortion/ nodularity

causes the progression of CF-associated liver disease to end-stage cirrhosis in some patients but not in others is still an enigma [10, 11, 12].

OBJECTIVE

The aim of this study was to analyze the prevalence of liver cirrhosis and portal hypertension in our CF population and the clinical and genetic characteristics of these patients.

METHODS

The case-notes of all 96 patients older than 2 years, presenting to CF center at the University Children's Hospital, which is the national CF center in Macedonia, were reviewed. The diagnosis of CF was made on the basis of typical respiratory disease and/or pancreatic insufficiency, together with abnormal sweat tests (chloride >70 mmol/l) or the presence of two CFTR mutations. The majority of patients were genotyped.

For a number of years, screening for liver disease is a part of annual review of patients with CF older than 2-3 years at our center. The assessment involves clinical, biochemical and ultrasonographic evaluation of the liver and the spleen.

Clinical assessment: the size of the liver and its consistency and the presence of splenomegaly were noted.

Laboratory examination: laboratory tests included serum liver enzymes (aspartate aminotransferase – AST, alanine aminotransferase – ALT, alkaline phosphatase – ALP, gamaglutamyl transpeptidase – GGT) and synthetic liver function tests (albumin, bilirubin levels, prothrombin time). The results were considered abnormal if at least two serum liver enzyme levels were higher than 1.5 times of the upper limit of normal: AST>52 IU/L, ALT>72 IU/L, GGT>78 IU/L, ALP>400 IU/L. A complete blood count was routinely performed to evaluate for the sings of hypersplenism.

Ultrasound assessment: included evaluation of liver echo texture, splenic size and portal vein diameter. A grading scheme of liver parenchymal appearances in CF at ultrasonography was presented in Table 2 [13]. The frank liver cirrhosis based on ultrasound criteria was defined by findings of distinct heterogeneity of liver parenchyma and nodular liver surface (regenerative nodules).

Liver biopsy was not included in the study protocol for liver cirrhosis; however, 5 patients with the ultrasound defined cirrhosis underwent this procedure. Upper gastrointestinal endoscopy was performed only in patients with portal hypertension for the evaluation of the presence of esophageal varices.

Portal hypertension was defined as any of the following: presence of splenomegaly detected on physical examination or ultrasonography, dilated collaterals of portal veins, reversed blood flow in portal veins, and endoscopically visualized esophageal varices.

Liver failure was defined by the presence of at least two of the following criteria: decreasing of albumin level <30 g/L, prolonged coagulation prothrombin time >3 seconds over normal, increasing bilirubin level >50 μmol/L, and development of ascites.

The following data were collected from the medical history of patients with liver cirrhosis: sex; current age, age of diagnosis of liver cirrhosis and/or portal hypertension; CFTR genotype; pancreatic functional status; current pulmonary function – forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) expressed as percentage of predicted values for weight, height and age; current nutritional status expressed as standard deviation score (Z score) for weight (zW), height (zH), and body mass index (BMI).

RESULTS

Out of all 96 patients older than 2 years that were followed at our CF center, 16 patients (9 males and 7 females) were found to have frank liver cirrhosis based on ultrasound criteria. The diagnosis of liver cirrhosis was confirmed by the liver biopsy findings in 5 patients. Two of them underwent this procedure at the age of 14, before the diagnosis of CF was established. In all cases, there was an evidence of cirrhosis or severe fibrosis. Portal hypertension was present in three patients, according to predefined criteria (splenomegaly, hypersplenism, esophageal varices on endoscopy). No CF patient had clinical and laboratory signs of decompensate cirrhosis and liver failure.

The median age of diagnosis of liver cirrhosis associated with CF was 8.5±3.8 years. It is important to emphasize that the diagnosis of liver cirrhosis with portal hypertension was made in two cases at the age of 14 and 15 years, respectively, because of misdiagnosed CF, although the patients had manifested symptoms of malabsorption, malnutrition and chronic pulmonary disease. The earliest age of diagnosis of liver cirrhosis in CF patient was in 2.5-year old girl with enormous hepatomegaly, and also with

delayed diagnosis of CF. Liver biopsy findings in this case indicated severe fibrosis, associated with the significant fatty infiltration of liver.

Clinical characteristics of the patients with CF-associated liver cirrhosis were reported in Table 3. Pancreatic insufficiency was present in all patients with CF-associated liver cirrhosis. Current nutritional status was well preserved in majority of regularly followed patients with cirrhosis related to CF. CF patients in the group with liver cirrhosis generally had mild-to-moderate lung disease, with average FVC and FEV_1 values of 97.1±16.5% of predicted and 87.9±23.5% of predicted, respectively. Nine patients in the group with cirrhosis had chronic *Pseudomonas aeruginosa* lung infection for many years, what is unfavorable prognostic parameter.

The results from biochemical evaluation of liver injury and function which included serum AST, ALT, GGT, ALP, albumin, bilirubin level, and prothrombin time, have shown low sensitivity and correlation with the ultrasonographic findings. Six patients with frank liver cirrhosis based on ultrasound, have never had evidence of any biochemical abnormalities in liver functional tests. The average values of the most recent biochemical tests in patients with liver cirrhosis were presented in Table 4.

Genetic analysis of the patients with CF-associated liver cirrhosis showed much higher frequency of F508del mutation in the group with cirrhosis (90.6%) in comparison with the frequency of the most common CFTR mutation in general CF population in Macedonia (69.2%). Molecular basis of CF in patients with cirrhosis was shown in Table 5. All patients in group with cirrhosis were either F508del homozygous (13) or compound heterozygotes for F508del and other severe mutation (3). Therefore, the patients with CF-associated liver cirrhosis had severe mutations associated with pancreatic insufficiency and more severe clinical course of the disease.

Table 3. Demographic and clinical characteristics of patients with CF-related liver cirrhosis

Variable	Value*
Current age (years)	17.7±6.8
Male/female	9/7 (56.3/43.7)
Age at diagnosis of liver cirrhosis	8.5±3.8
Pancreatic insufficiency	16 (100.0)
Z score for weight	-0.40±1.24
Z score for height	0.83±1.02
BMI (kg/m^2)	20.1±2.3
FVC (% predicted)	97.1±16.5
FEV_1 (% predicted)	87.9±23.5

* Values are expressed as mean±SD or number of patients (%).

Table 4. Laboratory parameters of patients with CF-related liver cirrhosis

Parameter	Mean±SD
Bilirubin (μmol/l)	16±6.8
AST (IU/L)	39.4±19.9
ALT (IU/L)	50.3±21.8
GGT (IU/L)	68±54.8
ALP (IU/L)	259.1±97.1
Albumin (g/L)	42.1±3.5
Prothrombin time (sec)	13.5±0.8

Table 5. Genotype of patients with CF-related liver cirrhosis

Genotype	No
F508del/F508del	13
F508del/G542X	1
F508del/1811+1G>C	1
F508del/Unknown	1

DISCUSSION

Recent advances in treatment and management of pulmonary complications, development of dedicated, multidisciplinary CF clinics and improved modes of nutrition have greatly improved the life expectancy of CF patients. As a result, chronic liver disease has become an important issue among patients with CF and its severity may determine the prognosis of this group. The reported prevalence of liver disease among CF patients ranges between 9% and 37%, depending on the study and criteria for defining the liver disease [11, 14, 15, 16]. Higher prevalence has been reported in studies in which liver disease had been actively searched for and diagnosed through a combination of diagnostic tools (clinical, biochemical, ultrasonographic evaluation). Because there are no sensitive diagnostic markers of liver involvement in CF, the actual prevalence might be even higher. In this context, the postmortem autopsy studies of CF individuals reported that the histological findings of focal biliary cirrhosis were present in 27% of children and 72% of adults [17, 18]. Prevalence seems to increase through childhood into mild-adolescence, with no significant increase thereafter [15]. A large majority of patients in our study developed liver cirrhosis during the first decade of life. This suggests that, for CF patients who will develop liver cirrhosis, the mechanism and risk factors of liver damage are already present in early childhood.

Therefore, some patients have progressive liver disease and develop cirrhosis with portal hypertension and rarely liver insufficiency, while sizeable proportion of patients may have only slight changes that remain stable life-long. Intrinsic abnormalities in the liver of individuals with CF reflect loss of CFTR (Cl^- channel) function on the apical membrane of cholangiocytes. This dysfunction is predicted to result in defective bile flow and associated with the cholangiocyte-inducted inflammatory response with activation and proliferation of hepatic stellate cells, which results in cholangitis and fibrosis in focal portal tracts [7, 9]. Although most CF patients have some degree of liver dysfunction and focal biliary cirrhosis, only 3%-5% of CF patients develop severe, end-stage liver disease [19].

The vast majority of CF patients that develop CF-related liver disease carry two "severe" (pancreatic insufficient) alleles of CFTR, so it is clear that carrying a mutation with some residual function ("mild", pancreatic sufficient mutations) provides relative protection against the development of the liver cirrhosis. Some authors found liver disease more often in homozygotes with the most common mutation, F508del, or other mutations associated with the pancreatic insufficiency, although studies failed to re-

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veal any relationship with the specific CFTR mutations [11, 20, 21]. In our study, the majority of CF patients with cirrhosis were F508del homozygous (81%), and a smaller proportion was compound heterozygotes for F508del and other "severe" mutation, associated with the complete loss of CFTR function. In one patient with liver cirrhosis the genotype was not completely defined (F508del/Unknown). All patients in cirrhosis group had pancreatic insufficiency. Accordingly, our data support the fact that patients with the pancreatic insufficiency and "severe" CFTR mutations, especially F508del, are exposed to higher risk of liver cirrhosis. Liver cirrhosis together with the pancreatic insufficiency is a component of the severe CF phenotype.

However, CF patients with the same CFTR genotype, including those homozygous for F508del, exhibit a range of liver diseases, strongly suggesting that non-CFTR genetic factors or possibly environmental factors (nutritional deficiencies, drug hepatotoxicity, infections) may be involved in the pathogenesis and progression of liver disease in CF. A small fraction (~5%) of patients with CF develops severe liver disease characterized by cirrhosis with portal hypertension; thus, other modifying genes outside of CF locus are believed to contribute to risk of developing severe liver disease [19, 22]. Candidate modifying genes, including genes for α_1-antitrypsin or α_1-antiprotease (SERPINA 1), angiotensin-converting enzyme (ACE), glutathione S-transverase (GSTP1), mannose-binding lectin2 (MBL2) and transforming growth factor β1, have been currently investigated [19]. It has been hypothesized that CF patients would be at increased risk of hepatic fibrosis if they also carried mutations in other genes pertinent to hepatic inflammation, oxidative stress, or fibrosis. Discoveries in this field may clarify which CF patients are at significant risk of developing severe liver disease.

Further evidence of genetic influence has been provided from HLA studies which have shown that the HLA haplotype B7-DR15-DQ6 is associated with an increased risk of the chronic liver disease in male patients with CF, implicating a possible immune pathogenesis of hepatobiliary injury in addition to the CFTR defect. It is likely that such immune mechanisms are secondary phenomenon of the obstructive biliary lesions, and may be important in determining the extent of liver damage [7].

It has been suggested that early therapy may prevent progression of CF-related liver disease [23]. Unfortunately, early recognition of liver disease in CF is not easy because its onset is often insidious and the clinical, biochemical and other indicators are relatively insensitive. Many patients with cirrhosis caused by CF are well compensated and completely asymptomatic and may even have normal liver blood tests. In our study, six patients with the liver cirrhosis have never had evidence of any biochemical abnormalities in liver functional tests. Therefore, regular screening for liver disease and identification of patients with the liver involvement, as well as early therapeutic intervention is of great importance in management of CF patients.

Screening for liver disease is a part of annual review of patients with CF older than 2-3 years at our center, for many years. The screening includes regular physical examination of liver and spleen, with special attention to the liver span, edge, and consistency; liver functional tests, and annual ultrasonography of the liver, biliary tract, gallbladder, spleen and hepatic vasculature. Implementation of screening program for liver disease is an important step in targeting population for early intervention and prophylactic treatment. The policy of examining only the patients with the abnormal liver function test results or those who are symptomatic fails to detect a number of young patients who clearly have abnormal echo texture of the liver, some of whom may progress to more severe liver disease. All patients with the liver cirrhosis and portal hypertension in our group (N=3) were with delayed diagnosis of CF. Portal hypertension was already established in two patients at the time of diagnosis of CF (at the age of 14 and 15) and in one patient it developed in the course of disease.

Ultrasound is likely to remain the most practical and frequently used imaging modality for assessing the hepatobiliary system and diagnosis of liver cirrhosis. Ultrasonographic abnormalities of liver appearance were more frequent than biochemical abnormalities, and once present were more likely to be persistent. Liver biopsy and histological assessment of liver was not included in our study protocol. Needle biopsies of the liver were performed only in several patients. Liver biopsy may be the gold standard for diagnosis of liver disease and determine the extent of portal fibrosis or cirrhosis. Widespread use of an invasive technique with an imminent risk of hemorrhage is probably not acceptable, especially within the pediatric population [7, 24].

At present, oral ursodeoxycholic acid (UDCA) therapy, aimed at improving biliary secretion in terms of bile viscosity and bile composition, is the only available therapeutic approach in CF-related liver disease. In many studies, UDCA, a naturally occurring hydrophilic bile acid, has been shown to normalize liver enzymes, improve hepatobiliary scintigraphy and contribute to improvement of liver morphology [23, 25, 26, 27], but so far the effect of UDCA on the ultimate outcome of the disease has not been proven yet [8].

Our experience and evidence suggest that the use of UDCA in the early stages may abort or inhibit further progression of the liver fibrosis/cirrhosis and development of portal hypertension. All patients (N=13) with frank liver cirrhosis based on ultrasound criteria, but without portal hypertension, have been on regular therapy with UDCA for many years. Up to now, they have no clinical evidence of portal hypertension. Even more, liver cirrhosis did not have significant impact on the nutritional status and pulmonary function of these patients. CF patients with the liver cirrhosis tended to have mild-to-moderate lung disease, although nine patients in this group have had chronic *Pseudomonas aeruginosa* lung infection for many years. Only four patients with the liver cirrhosis had more advanced lung disease and required frequent hospitalization for intravenous therapy due to pulmonary exacerbations.

Liver transplantation is a treatment of choice for patients with the advanced CF-related liver disease and preserved pulmonary function (FEV_1>50%) [28]. The indication for liver transplantation considered a variety of fac-

tors including liver failure, hypersplenism, malnutrition, gastro-esophageal bleeding, and worsening pulmonary function [29, 30]. Most authors suggest that liver transplantation should be performed prior to the development of end-stage liver disease or overt pulmonary or other clinical decompensation [28].

CONCLUSION

With an improved survival of CF patients, the relative importance of liver disease has increased and it is now the second commonest cause of mortality from CF. Liver disease should be considered an early complication involving more than one fourth of CF patients. Active follow-up evaluation directed at its detection should be started early in the life, preferentially in patients with the pancreatic insufficiency and severe CFTR mutations, who are at higher risk of developing this CF complication. However, only a small fraction (~5%) of patients with CF develops severe liver disease characterized by cirrhosis with portal hypertension; thus non-CFTR genetic variability may contribute to risk of contracting severe liver disease. Patients identified by screening procedures are expected to have slower progress of disease than patients who initially draw attention due to their symptoms.

REFERENCES

1. Rowntree R, Harris A. The phenotypic consequences of CFTR mutations. Ann Hum Genet. 2003; 67:471-85.
2. Jentsch TJ, Stein V, Weinreich F, Zdebik AA. Molecular structure and physiological function of chloride channels. Physiol Rev. 2002; 82:503-68.
3. de Gracia J, Mata F, A´lvarez A, Casals T, Gatner S, Vendrell M, et al. Genotype-phenotype correlation for pulmonary function in cystic fibrosis. Thorax. 2005; 60:558-63.
4. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989; 245:1066-73.
5. Cystic Fibrosis Mutation Database. The Cystic Fibrosis Genetic Analysis Consortium. Available from: www.genet.sickkids.on.ca/cftr/.
6. Castellani C, Cuppens H, Macek Jr M, Cassiman JJ, Kerem E, Durie P, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros. 2008; 7:179-96.
7. Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. J Pediatr Gastroenterol Nutr. 1999; 28(Suppl):1-13.
8. Feranchak AP. Hepatobiliary complications of cystic fibrosis. Curr Gastroenterol Rep. 2004; 6:231-9.
9. Colombo C. Liver disease in cystic fibrosis. Curr Opin Pulm Med. 2007; 13:529-36.
10. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros. 2011; 10(Suppl 2):S29-S36.
11. Wilschanski M, Rivlin J, Cohen S, Augarten A, Blau H, Aviram M, et al. Clinical and genetic risk factors for cystic fibrosis-related liver disease. Pediatrics. 1999; 103:52-8.
12. Moyer K, Balisteri W. Hepatobiliary disease in patients with cystic fibrosis. Curr Opin Gastroenterol. 2009; 25:272-8.
13. Williams SM, Goodman R, Thomson A, McHugh M, Lindsell DRM. Ultrasound evaluation of liver disease in cystic fibrosis as part of an annual assessment clinic: a 9-year review. Clin Radiol. 2002; 57:365-70.
14. Lamireau T, Monnereau S, Martin S, Marcotte JE, Winnock M, Alvarez F. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol. 2004; 41:920-5.
15. Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology. 2002; 36:1374-82.
16. Fustik S, Trajkovska M, Jakovska T, Spirevska L, Josifovska T, Koceva S. Screening for liver disease in cystic fibrosis: analysis of clinical and genetic risk factors for its development. Turk J Pediatr. 2008; 50:526-32.
17. Oppenheimer EH, Esterly JR. Hepatic changes in young infants with cystic fibrosis: Possible relation to focal biliary cirrhosis. J Pediatr. 1975; 86:683-9.
18. Vawter GF, Shwachman H. Cystic fibrosis in adults: An autopsy study. Pathol Ann. 1979; 14:357-82.
19. Bartlett JR, Friedman KJ, Ling S, Pace RG, Bell SC, Bourke B, et al.; for the Gene Modifier Study Group. Genetic modifiers of liver disease in cystic fibrosis. JAMA. 2009; 302:1076-83.
20. De Arce M, O'Brien S, Hegarty J, O'Mahoney SM, Cashman SM, Martinez A, et al. Deletion F508 and clinical expression of cystic fibrosis-related liver disease. Clin Genet. 1992; 42:271-2.
21. Wilschanski M, Durie PR. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. Gut. 2007; 56:1153-63.
22. Castaldo G, Fuccio A, Salvatore D, Raia V, Santostasi T, Leonardi S, et al. Liver expression in cystic fibrosis could be modulated by genetic factors different from the cystic fibrosis transmembrane regulator genotype. Am J Med Genet. 2001; 98:294-7.
23. Colombo C, Battezzati PM, Padda M, Bettinardi N, Giunata A. Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. Hepatology. 1996; 23:1484-90.
24. Mueller-Abt PR, Frawley KJ, Greer RM, Lewindon PJ. Comparison of ultrasound and biopsy findings in children with cystic fibrosis related liver disease. J Cyst Fibros. 2008; 7:215-21.
25. Nausia-Avranitakis S, Fountoulaki M, Economou H, Xefteri M, Galli-Tsinopoulou A. Long-term prospective study of the effect of ursodeoxycholic acid on cystic fibrosis related liver disease. J Clin Gastroenterol. 2001; 32:324-8.
26. Siano M, De Gregorio F, Boggia B, Sepe A, Ferri P, Buonpensiero P, et al. Ursodeoxycholic acid treatment in patients with cystic fibrosis at risk for liver disease. Dig Liver Dis. 2010; 42:428-31.
27. Desmond CP, Wilson J, Bailey M, Clark D, Roberts SK. The benign course of liver disease in adults with cystic fibrosis and the effect of ursodeoxycholic acid. Liver Int. 2007; 27:1402-8.
28. Melzi MJ, Kelly DA, Colombo C, Jara P, Manzanares J, Colledan M, et al. Liver transplantation in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. Transpl Int. 2006; 19:726-31.
29. Nash KL, Collier JD, French J, McKeon D, Gimson AES, Jamieson NV, et al. Cystic fibrosis liver disease: to transplant or not to transplant? Am J Transplant. 2008; 8:162-9.
30. Colombo C, Costantini D, Rocchi A, Romano G, Rossi G, Bianchi ML, et al. Effects of liver transplantation on the nutritional status of patients with cystic fibrosis. Transpl Int. 2005; 18:246-55.

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Цироза јетре и портна хипертензија код цистичне фиброзе

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КРАТАК САДРЖАЈ

Увод С побољшањем очекиваног преживљавања особа са цистичном фиброзом, они се могу суочити са бројним медицинским компликацијама.

Циљ рада Циљ овог рада био је да се анализирају преваленција цирозе јетре код особа са цистичном фиброзом и клиничке и генетске одлике ових болесника.

Методе рада Сви болесници старији од две године (96) били су испитани због болести јетре. Цироза јетре је дефинисана ултразвучним налазима јасне хетерогености јетреног паренхима и нодулиране површине јетре и/или налазом биопсије јетре. На портну хипертензију су указивали повећана слезина, проширење портних вена и поремећен портни венски проток. Анализирани су клинички и генетски подаци болесника.

Резултати Цироза јетре је установљена код 16 болесника, од којих су три имала портну хипертензију. Сви болесници су имали инсуфицијенцију панкреаса. Нутритивни статус, изражен као стандардна девијација (*Z score*) за тежину (*zW*), висину (*zH*) и индекс телесне масе (*BMI*), био је: *zW*=-0,40±1,2; *zH*=-0,83±1,0; *BMI*=20,1±2,3 *kg/m*^{2}. Болесници са цирозом јетре имали су углавном благо до умерено обољење плућа, с просечним вредностима *FVC* и *FEV*$_1$ од 97,1±16,5% и 87,9±23,5% од предвиђених. Генетска анализа је показала високу фреквенцију мутације *F508del* у групи болесника са цирозом јетре (90,6%).

Закључак Преваленција цирозе јетре код наших болесника старијих од две године са цистичном фиброзом је 16,6%. Болесници са инсуфицијенцијом панкреаса и с тешким мутацијама *CFTR*, посебно *F508del*, изложени су већем ризику за развој цирозе јетре. Цироза јетре нема значајан утицај на функцију плућа и нутритивни статус све до крајњег стадијума болести јетре.

Кључне речи: цистична фиброза; мутације *CFTR* гена; цироза јетре; портна хипертензија

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