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Liver disease in cystic fibrosis patients in a tertiary care center in Saudi Arabia

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ABSTRACT

Background: Internationally, Cystic fibrosis-associated liver disease (CFLD) is considered the third leading cause of death, following lung disease and transplantation complications.
Aims: To identify the prevalence of CFLD in cystic fibrosis (CF) patients.
Methodology: A retrospective chart review for all patients with CF liver disease from a tertiary care center.
Result: A total of 341 CF patients were included. The mean age at the diagnosis of liver disease is 13.5 (7.6) years.The first elevated ALT was reported in 190/341 patients (56%), elevated AST in 124 patients (36%), elevated alkaline phosphatase (ALP) in 166 patients (49.1%), elevated GGT in 57 patients (23%), and elevated bilirubin in 24 patients (7%). There was an improvement of the liver enzyme values during the follow-up period, *P*-value = (<0.05).Ultrasound liver assessments were performed in 258/341 patients (75.7%). One hundred and twelve patients (43%) had abnormal findings. In 14 patients (5.4%), assessment exhibited advanced liver disease (liver cirrhosis and periportal fibrosis). Out of 190 patients, who were given ursodeoxycholic acid for elevated liver enzymes, 180 (94.7%) exhibited improvement. One patient underwent liver transplant at the age of 12. Four patients were submitted for liver biopsy; periportal fibrosis was observed in 4 patients (1.6%), and liver cirrhosis by ultrasound (US) in 10 patients (4%).
Conclusion: Patients with CF should be screened early for liver enzymes, and should undergo the US study to detect liver disease at early stages and to prevent its progression.

1. Introduction

Cystic fibrosis is multisystem disorder of autosomal recessive inheritance in which there is an underlying defect of ion transport [1]. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) cause it [2]. This leads the body to secrete dehydrated mucus within the upper and lower respiratory tracts, which causes infection, inflammation, and lung tissue destruction. It affects the digestive system by obstructing the flow of bile to the small intestine, in addition to pancreatic insufficiency, gallstones, and chronic liver disease [3]. The availability of different modalities of diagnostic tools that enable early detection and initiation of treatment has permitted elongation of the lifespan of CF patients. As a result, more complications have started to appear [4,5].

Following lung disease and complications linked to lung transplantation, cystic fibrosis-associated liver disease (CFLD) is the third leading cause of death in CF patients [2].

In CF patients, severe liver disease can occur in mid-childhood

Abbreviations: CF, Cystic Fibrosis (*CFTR*) = Cystic Fibrosis Transmembrane Conductance Regulator Gene, Mutations.CFLD; Cystic fibrosis liver diseaseLD, Liver diseaseALT; alanine aminotransferaseAST, aspartate aminotransferase APRi; AST to platelet ratio index FIB-4, Fibrosis-4 scoring system US; Ultrasound SD, Standard Deviation ALP; alkaline phosphatase GGT, gamma glutamyl transpeptidase, LFTs; Liver function tests,INR, International normalized ratio.

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(around 10 years of age) and is more common in boys than in girls [6]. Abnormal platelet counts, aspartate aminotransferase-to-platelet ratio index (APRi), and fibrosis-4 (FIB- 4) scores are more common in patients with esophageal varices and those who receive liver transplants [6].

The prevalence of CFLD has been estimated to be between 26% and 45% [4]. It is relatively frequent and may appear as an early complication of CF. Patients with a history of meconium ileus, who belong to the male sex, or with a severe genotype should be screened in their first decade of life. CFLD can progress rapidly, necessitating a liver transplant [7]. CFLD is difficult to diagnose because of its subtle signs; owing to the lack of sensitivity and specificity of biochemical values and imaging studies to detect the liver involvement before the development of symptoms of cirrhosis with portal hypertension. Identification of a CF patient's laboratory values that are associated with the risk of cirrhotic liver disease at an early stage is valuable to prevent further liver damage [8]. There are many reported definitions of liver disease in CF: 1- a combination of splenomegaly by clinical assessment or US, and macro-nodularity of the liver on US [8], 2- US findings including distinct heterogeneity of liver parenchyma with a nodular liver surface [9], and 3-hepatomegaly or hepatosplenomegaly, abnormalities of liver function tests, abnormalities on liver ultrasound, and liver biopsy [10].

In a study reported by Williams [11], a total of 725 ultrasound examinations were performed. At least one US finding of abnormality in liver echotexture was found in 60 patients, whereas the findings persisted in 39 patients. Seven patients developed cirrhotic changes, and an additional 15 patients had persistent splenomegaly.

In 176 examinations, there was a disparity between US finding and aspartate aminotransferase (AST). There were persistent abnormalities of liver echotexture and splenomegaly with a normal range of AST in five patients. Ultrasound assessment was compared in the same study between 84 CF patients in the liver disease group (LD) and the nonliver disease group (NLD) [11]. A significant difference was noticed in spleen length, but no difference in the liver volume [11].

In another study from Australia, a cohort of 62 patients [12] underwent a prospective evaluation between 1994 and 2009. Liver involvement (clinical, laboratory, and/or ultrasound abnormalities) was evident in seven pediatric patients (age <18 years) with CF at a median age of 7 years, occurring in the first decade of life in five children [12]. One patient had an early severe presentation at 3 years of age. Three patients presented with clinical signs of liver disease, including isolated hepatomegaly in one patient and hepatosplenomegaly in two other patients. Biochemical abnormalities such as increased levels of alanine aminotransferase (ALT), AST, and/or gamma-glutamyl transpeptidase (GGT) were present in six patients (three with AST/ALT >1.5 upper limit). In one patient, liver enzymes were persistently normal. Hepatic parenchyma heterogeneous echogenicity was the most commonly found abnormality in US (6/7); with nodularity additionally present in 2/7 patients, nodular liver edge in 1/7 patients, and signs of portal hypertension in 2/7 patients. One patient had homogeneous echogenicity of the hepatic parenchyma [12].

At present, the therapeutic drug of choice for CFLD is ursodeoxycholic acid which has been hypothesized to improve bile flow, thereby decreasing the incidence of cirrhotic liver disease [9]. This therapeutic effect has never been proven efficacious in randomized controlled trials, but is nevertheless used by CF clinicians globally. For advanced decompensated cirrhosis, liver transplantation or combined liver–lung transplantation is a suitable option with promising outcomes [3].

This study aimed to compare it with an earlier study [3] to find out if the introduction of early treatment will improve the incidence of liver disease, and also what factors cause a CF patient to become more likely to experience CFLD.

2. Methodology

2.1. Definitions

The diagnosis of CF was established in all patients according to one of the following criteria: 1- Patients with typical pulmonary and/or gastrointestinal symptoms, and a family history of CF; in addition to sweat chloride concentration >60 mEq/L, and/or two-pathologic CFTR mutations on each chromosome.

2.2. Patient population

A retrospective chart review for 341 patients with CF was confirmed for the period from 1986 to January 2018. The variables that were reviewed included: serum liver enzyme (ALT, AST, GGT, ALP), synthetic liver function tests (bilirubin and albumin), and US findings, in addition to the type of treatment received. Ultrasound abnormalities that are consistent with liver involvement include liver parenchymal abnormalities and evidence of periportal fibrosis [1].

2.3. Definition of high liver enzymes

Elevated ALT and AST > 65 IU/L, GGT > 35 IU/L, ALP > 350 IU/L, bilirubin 25, and abnormal albumin, if less than 20.

2.4. Ethical considerations and statistical method

After the study, the advisory committee gave their ethical approval. The Declaration of Helsinki was followed, along with good clinical practice guidelines. The principal investigator supervised the data collection and entry process. All data required were obtained by retrospective chart review, saved in the pediatrics research unit, and were only accessible by the principal investigator and the clinical research coordinator assigned. All data were kept strictly confidential. Each patient was assigned a study number, and all of the patients' data were anonymously entered into the specified data sheet (EXCEL). The Department of Biostatistics Epidemiology and Scientific Computing (BESC) performed the statistical analysis. The frequency of events was obtained by mean (SD), with simple descriptive analysis.

2.5. CFTR identification

This was performed according to previously mentioned procedures [13].

3. Results

A total of 341 cystic fibrosis patients were included in our study. One hundred and seventy-seven (52%) were females, and164 (48%) were males at the time of data entry; 304 (89%) patients are alive and 37 (11%) have died. Saudi Arabia's eastern region contributed the highest number of CF patients – 154 (45.2%). Three readings of each biochemical results were obtained; the first elevated ALT was reported in 190/341 patients (56%); AST was elevated in 124 patients (36%), ALP was elevated in 166 patients (49.1%), elevated GGT was noted in 57 patients (23%), and bilirubin was elevated in 24 patients (7%). There was marked improvement and normalization of the liver enzyme values during the follow-up period in most patients (Table 1), *P*-value = (<0.05). Ultrasound liver assessments were performed in 258/341 patients (75.7%). One hundred and

twelve patients (43%) had abnormal findings (Table 2). In 14 patients (5.4%), evidence of advanced liver disease (liver cirrhosis and periportal fibrosis) was noted. (Table 3). In a total of 190 patients who were given ursodeoxycholic acid for elevated liver enzymes, 180 (94.7%) demonstrated improvement and normalization of the enzyme level. One patient underwent a liver transplant at the age of 12 years owing to complicated liver disease with esophageal varices. Four patients underwent liver biopsy; periportal fibrosis was observed in 4 patients (1.6%)and liver cirrhosis in 10 patients by US studies (4%) (Table 2). Two patients developed advanced liver disease by US despite normal biochemical values, and three patients developed cirrhosis with elevated GGT only (Table 2).

For patients with liver cirrhosis, the most common identified CFTR gene mutations were c.1418delG [14,15] in 3/12 (30%), followed by c.1521_1523delCTT [15–17] in 3/10 (30%) (Table 3).

4. Discussion

In this retrospective study, we identified liver involvement in CF patients by an abnormal biochemical result and/or the abnormal US of the abdomen. Previous studies have revealed that patients with CF, who were diagnosed earlier, have a higher risk of developing severe liver disease; suggesting that liver involvement may be secondary to a severe mutation [5,18,19]. Male gender is considered as one of the risk factors for developing liver disease [19]. In our study, there was no gender difference in developing liver disease.

Abnormalities in liver function tests (LFTs) are insensitive for detecting severe liver disease and fibrosis in children with suspected CFLD, and therefore, are not effective for detecting or assessing fibrosis progression [20]. Hepatomegaly, alone or in conjunction with splenomegaly, has a prevalence rate of 4%–40% in studies that use them as markers for liver disease. Damage to intrahepatic bile ducts that results in portal tract fibrosis with preserved hepatic architecture is a hallmark of CFLD. Liver biopsy is an invasive procedure. Furthermore, the patchy distribution of histopathology in CFLD makes liver biopsy problematic as it is the golden standard [20]. The serial use of US in diagnosis will recognize only a small number of patients with liver disease who have normal biochemical results. According to a reported study, 126 of 725 patients (17.4%) above 9 years had abnormal US findings in combination with the normal range of AST [11]. Another study from Macedonia reported six patients with frank liver cirrhosis without evidence of any biochemical abnormalities [9]. Similar to our study, 2/10 (20%) patients with confirmed advanced liver disease by US had normal biochemical results.

A cohort study from the Netherlands [8] proposed that a persistently high normal GGT was strongly linked to CFLD diagnosis; the study included 277 confirmed CF patients. A total of 19 patients (7%) had macro-nodularity of the liver with splenomegaly. GGT was discovered to be elevated in 79% of CFLD patients after documenting the result after two years preceding the diagnosis of CFLD; however, it was rarely accompanied by an elevation in ALT [8]. Similar to our study, two patients developed advanced liver disease, but they had normal ALT and AST.

Another research group suggested that in patients with a history of meconium ileus, belonging to the male sex, or with a serious genotype, CFLD should be screened in the first decade of life [7]. It can progress quickly in some patients, necessitating liver transplantation [7].

E Fagundes [19] reported that the age variable remained significant when included in a continuous form ($P = .014$); the younger the patient at diagnosis, the higher was the risk of developing clinically significant liver disease. In the multivariate analysis performed in this sample, variables commonly associated liver disease with sex, pancreatic insufficiency, and meconium ileus that were not statistically important [18]. Patients diagnosed at a young age

Table 1
Patients with elevated liver enzyme Total: 341 patients.

Liver enzyme test	Age yr (SD)		No. of patients	1st liver enzyme level	No. of patients	Mid period of follow-up levels	No. of patients	Last follow-up levels
ALT	5 (5.7)	Total	341	41.4 (67.8)	311	30.3 (30.1)	225	23.8 (18.5)
		Nor	134	17.8 (4.6)	171	17.7 (4.3)	126	17.1 (4.4)
		Abn	190	61 (85.9)	121	51.7 (39.4)	69	43.1 (22.7)
AST	5.9 (6)	Total	348	52.5 (100)	292	38.6 (35)	211	28.7 (16.2)
		Nor	224	31.9 (8.6)	225	28.8 (8.4)	185	24.6 (8.3)
		Abn	124	89.8 (160.9)	64	74.4 (61)	24	61.9 (23.1)
ALP	–	Total	338	251 (114)	300	243.8 (256.3)	219	210.3 (154.9)
		Nor	154	180.3 (38.1)	138	173.6 (38.2)	125	166.2 (42)
		Abn	166	335 (100.7)	134	350.6 (351.8)	62	370.1 (205.7)
GGT	–	Total	245	52 (102.2)	171	40.5 (96)	103	32.3 (72.6)
		Nor	137	21 (8.5)	84	18.2 (7.4)	59	18.6 (7.7)
		Abn	57	165.6 (167.7)	29	171 (185.7)	10	192 (166.2)
Bilirubin	4.7 (5.5)	Total	341	11 (33.5)	–	–	312	8.5 (17.8)
		Nor	317	5.5 (3.6)	7	9.3(2.3	286	6.3 (3.6)
		Abn	24	84.3 (101.7)	–	–	12	67.8 (68)
Albumin	4.6 (5.5)	Total	341	38.6 (7.4)	316	40.2(6.2)	249	40.1 (7)
		Nor	178	43 (2.4)	204	43.5 (2.3)	153	43.8 (2.5)
		Abn	160	33.2 (6.6)	130	35 (6)	93	33.5 (6)

Legend.
ALT- Alanine aminotransferase 10–25 u/l.
AST- Aspartate aminotransferase 10–45 u/l.
ALP- Alkaline phosphatase 100–240 u/l.
GGT- Gamma glutamyl transpeptidase 12–49 u/l.
Bilirubin- 0–21 μmol/l.
Albumin- 40–50 g/dl.
All- All.
Nor- Normal.
Abn- Abnormal.
- Number.
Yr – Year.
SD = Standard deviation.
p-value= <0.05.

Table 2
Ultrasound abdomen (US) findings Total patients: 258.

Variable	1st US result Total 258	
	Number[a]	%
Normal	146	56.6
Mild hepatomegaly	42	16.3
Increase in echogenicity of the liver (homogenous- heterogeneous)	63	24.4
Fatty infiltration	38	14.7
Peri portal fibrosis	4	1.6
Cirrhosis- very coarse liver texture- very diffuse irregular pattern - increase irregularity	10	3.9
Mild diffuse hepatic steatosis	1	0.4

Legend: 112/258 patients had abnormal ultrasound findings Patients may have overlap of more than one US finding.

Table 3
Details of CFTR for patients with CF liver cirrhosis Total: 10 patients (17) 10 of our 112 patients with abnormal ultrasound had liver cirrhosis.

Pt	Sex	Age of CF Dx.	Age of CFLD	Age at follow up	Abn values	US abd.	Mutation	Nucleotide change	refSNP
1	F	5 Mon	3 Y	7 Y	NS	Ppf/NS	3120+1G > A	c.2988+1G > A	rs75096551
2	M	4 Y	9 Y	12 Y	All	C/NS	3120+1G > A	c.2988+1G > A	rs75096551
3	M	1 Mon	4 Y	10 Y	GGT	C/NS	3120+1G > A	c.2988+1G > A	rs75096551
4	M	1 Y	16 Y	17 Y	GGT	C/NS	3120+1G > A	c.2988+1G > A	rs75096551
5	M	2 Y	2 Y	13 Y	All	C/SpM	p.His139Leu	c.416A > T	rs76371115
6	F	9 Y	9 Y	10 Y	NS	C/SpM	p.Gly473GlufsX54	c.1418delG	rs397508205
7	M	1 Y	10 Y	18 Y	GGT	C/SpM	p.Gly473GlufsX54	c.1418delG	rs397508205
8	F	3 Mon	14 Y	17 Y	All	C/SpM	p.Gly473GlufsX54	c.1418delG	rs397508205
9	F	5 Y	5 Y	7 Y	All	Ppf/SpM	p.Phe508del	c.1521_1523delCTT	rs113993960
10[a]	F	1 Y	9 Y	21 Y	All	C/NS	-	-	–

Legends (Table 3).
CF: Cystic Fibrosis.
US: Ultrasound study.
Pt: Patient.
CFLD: Cystic fibrosis liver disease.
M: Male.
F: Female.
Dx: Diagnosis.
Dis: Disease.
NS: Normal Spleen.
Abd: Abdomen.
C: Cirrhosis.
Abn: Abdormal
SpM: Splenomegaly.
HepaM: Hepatomegaly.
Lab: laboratory values.
Y: Years.
Mon: Months.
Ppf: Periportal fibrosis.
GGT: gamma glutamyl transpeptidase.
refSNP: Reference single-nucleotide polymorphism cluster ID.
All: All the liver enzymes are abnormal (ALT, AST, GGT..).
[a] Patient died before CFTR mutational identification.

and those with lower health status as measured by the Shwachman score have a greater risk of developing liver disease – which means that liver involvement could be part of a more severe form of the disease. These patients should be given more care in terms of liver disease screening and treatment with ursodeoxycholic acid earlier in case of abnormal findings [19].

Another study [10] depicted that 7 of 62 patients had CFLD and refractory variceal bleeding, whereas progressive hepatic dysfunction occurred in one patient – necessitating liver transplantation. All patients had c.1521_1523delCTT mutation [15,16] in addition to pancreatic insufficiency; no cases of meconium ileus were reported in this series. At an average age of 8 years (3–15 years), liver involvement became clinically evident. It presented as hepatomegaly or hepatosplenomegaly (3 cases), and/or abnormalities of liver function tests (3 cases), and ultrasound changes in the liver (7 cases) with reports of portal hypertension (2 cases).

In our study, 5/10 patients with liver cirrhosis had hepatosplenomegaly and 3/5 had the common Saudi mutation, c.1418delG (Table 3). The genetic analysis of our study revealed a high frequency of c.1418delG and c.1521_1523delCTT mutations in the group with cirrhosis 6/10 (60%). Our CF population had a 17% occurrence of liver cirrhosis. Patients with pancreatic insufficiency and severe CFTR mutations, especially c.1521_1523delCTT, had a higher risk of liver cirrhosis. Until it progresses to end-stage liver disease, the latter has no major effects on pulmonary function and nutritional status [10].

In the literature, over 2000 CFTR gene mutations have been identified [14–17]. Evidence of a phenotypic relationship with specific mutations in the CFTR gene has not been identified [3,5,7]. However, there is a well-established correlation between CFTR genotype and phenotype, and pancreatic insufficiency. In the United States and Europe, the most common CFTR mutation is c.1521_1523delCTT [16,17] (66%), whereas in the Middle East, the most common mutation is c.1418delG [13,15,16].

5. Conclusion

Patients who were diagnosed at a young age and those with a poorer clinical status as calculated by the Shwachman score, have a greater risk of developing clinically significant liver diseases – which means that liver involvement could be part of a more severe form of the disease. Such patients should be provided more consideration when it comes to liver disease screening and should be treated with ursodeoxycholic acid early in the course of the disease [20]. All young CF patients should be screened early for liver enzyme and subjected to US study to detect liver disease in its earliest stages to prevent progression [20].

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Visual abstract

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