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Liver disease in children with cystic fibrosis: observational study

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Abstract

Introduction: *Cystic fibrosis (CF) is a genetic disease of autosomal recessive inheritance, characterized by dysfunction of the exocrine secretion glands. The liver is an affected organ, which causes an increase in early morbidity and mortality.* **Objective:** *To evaluate liver disease in a group of children with CF.* **Material and methods:** *A total of 82 children with CF confirmed with genetic testing were included. Biochemical liver function tests and liver ultrasound were evaluated. The presence of fibrosis was estimated using the aspartato aminotransferasa to platelet ratio index (APRI) and correlation tests were performed.* **Results:** *59.8% (n = 49) of patients had elevated alanine aminotransferase. 30.5% (n = 25) showed an APRI suggestive of fibrosis. The correlation of APRI with alanino aminotransferase was 0.685 (p < 0.001) and with GGT 0.385 (p < 0.001). The prevalence of alterations in hepatic echogenicity was lower than biochemical alterations in transaminases.* **Conclusions:** *There is a high prevalence of liver disease at the diagnosis of CF and even a third of children could present with liver fibrosis. In this study, we found no difference in liver function tests according to liver ultrasound.*

Keywords: *Cystic fibrosis. Liver fibrosis. Transaminases.*

Introduction

Cystic fibrosis (CF) is a disease of genetic origin, with autosomal recessive inheritance that is diagnosed mainly in children. It is caused by pathogenic variants in the CF transmembrane conductance regulator (CFTR) gene. The main system affected is the respiratory tract and pancreas. There is also the involvement of the sweat glands, the intestine, the nasal mucosa, the salivary glands, and the reproductive system[1].

The liver is a frequently compromised organ[2], liver damage develops within the first 20 years of life and is usually stable, with a slowly progressive evolution[3]; however, some children may develop liver cirrhosis in early childhood or adolescence[4]. Determining the coexistence of liver disease is important, as it has a relevant implication in the short- and long-term prognosis of children with CF[5].

The objective of this study was to determine the prevalence and characteristics of liver disease by evaluating liver function tests in a group of children with CF at the time of diagnostic confirmation.

Methods

A retrospective analytical study included 82 children with a confirmed genetic diagnosis of CF, treated in the Pediatric Gastroenterology and Nutrition service at Instituto Nacional de Pedriatría (Mexico City, Mexico). Baseline liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltranspeptidase, alkaline phosphatase, albumin, lipids, bilirubin's,

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and INR) were collected. The cutoff point of the SAFETY study[6] was used for the detection of chronic liver disease in children, considering the elevation of alanino aminotransferase (ALT) > 22.1 U/L in girls and 25.8 U/L in boys. The aspartato aminotransferasa (AST) to platelet ratio index (APRI) was calculated using the formula proposed by Wai et al.[7]. (APRI = [patient AST level/AST upper limit normal] × 100/platelet count 10^9/L), which was interpreted: < 0.5 = no significant fibrosis, 0.5-1.5 = probable fibrosis, and > 1. 5 = significant fibrosis.

Statistical analysis

The distribution of normality was evaluated with the Kolmogorov–Smirnov test. Subsequently, descriptive statistics were performed. The means were compared with the Mann–Whitney U test and correlations were made with the Sperson test. Statistical significance was established with an alpha error < 0.05. The analysis was performed in the SPSS version 22 software.

Bioethics

The study complies with current bioethical regulations on international recommendations for research in humans and adheres to the research guidelines of the Instituto Nacional de Pedriatría.

Results

A total of 82 children diagnosed with CF were included. The median age at diagnosis was 10 months (interquartile range = 30). 59.8% (n = 49) of the patients had elevated ALT in the first biochemical evaluation after diagnosis, the means of the other liver function tests are presented in table 1.

Of 69.5% (n = 57) had APRI between 0-0.5 (without fibrosis), 24.4% (n = 20) had APRI between 0.5-1.5, and 6.1% (n = 5) had APRI > 1.5. The correlation of APRI with ALT was 0.685 (p < 0.001), with AST 0.804 (p < 0.001), and with GGT 0.385 (p < 0.001), no correlation was found with other liver function tests (Table 2). When comparing liver function tests according to sex, we did not find significant differences, nor a greater association of ALT elevation in boys or girls (p = 0.159).

The most frequent genetic mutations were F508del (n = 14) and G542X (n = 9), no difference was found between the two groups in the comparison of liver function tests.

The children included in this study underwent liver ultrasound and 39% (n = 32) had alterations consistent with changes in liver echogenicity; however, when comparing the liver function tests of the children with and without liver ultrasound alterations, no differences were found (Table 3).

Table 1. Liver function tests and biochemical parameters in children with cystic fibrosis

Parameters	Median and interquartile range
ALT	32 (41)
AST	49 (41)
ALP	194 (166)
GGT	33 (54)
Platelets	350,000 (187,000)
Albumin	3.30 (1.3)
INR	1.03 (0.20)
BT	0.57 (0.40)
BD	0.17 (0.22)
Vitamin D	18 (11)
CT	111 (48)
Triglycerides	98 (55)
APRI	0.34 (0.38)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase; INR: *International normalized ratio;* BT: total bilirubin; BD: direct bilirubin; CT: total cholesterol; APRI: AST to platelet ratio index.

Discussion

In this study, we found that more than half of the children with the confirmatory diagnosis of CF had elevated transaminases. It has been described that CF-associated liver disease occurs due to alteration in the cholangiocyte transport protein, which results in chronic cholangiopathy secondary to a reduction in ductal bile flow, bile chloride, and bicarbonate secretion due to CFTR dysfunction[8]. However, the mechanism of liver injury is considered to be multifactorial, including the CFTR genotype, non-CFTR genetic variability, abnormal intracellular interactions, abnormal cholangiocyte function, impaired bile secretion, and pathological stimulation of the innate immune response with an abnormal response to endotoxins[2,9].

The prevalence of liver disease in children with CF is varied and has been reported to occur in 5% to 68%, depending on the criteria used for its diagnosis[10,11]. Risk factors include male sex, the presence of severe

Table 2. APRI correlation tests with biochemical parameters and liver function tests

	ALT	AST	ALP	GGT	Albumin	Vit D
Correlation	0.685	0.804	0.47	0.385	–0.068	–0.248
p	< 0.001	< 0.001	0.675	< 0.001	0.547	0.043

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase.

Table 3. Comparison of liver function tests according to liver ultrasound abnormalities in children with cystic fibrosis

	Altered USG	Normal USG	p
ALT	56.16 ± 69	38.73 ± 32	0.393
AST	121.16 ± 195	39.86 ± 12	0.119
ALP	187.91 ± 87	177.40 ± 87	0.759
GGT	82.58 ± 41	41 ± 37	0.219
Platelets	347,000 ± 94,000	402,000 ± 138,000	0.250
Albumin	3.3 ± 0.9	3.2 ± 0.7	0.692
BT	1.3 ± 1	0.5 ± 0.29	0.72
APRI	1.1 ± 2.2	0.29 ± 0.17	0.164

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase; INR: *International normalized ratio*; BT: total bilirubin; APRI: AST to platelet ratio index.

mutations, the presence of the *SERPINE 1Z* allele, a history of meconium ileus, exocrine pancreatic insufficiency, and CF-associated diabetes[12]. In our study, we found no difference in the alteration of liver function tests according to sex. The most frequently reported mutations in patients were F508del and G542X, with no major difference in liver involvement observed according to the type of mutation.

In our study, we used the *APRI* to estimate the presence of liver fibrosis in children with CF. At present, there are different validated non-invasive methods to evaluate liver disease in the adult population[13] and some have been used in the pediatric age with different results. APRI has shown good diagnostic performance in establishing the diagnosis of fibrosis in children with NAFLD (AUROC 0.619, 95% CI 0.556-0.679, p < 0.001)[14]; however, it seems to be superior in establishing liver involvement in children with CF. A study that evaluated the usefulness of non-invasive methods for diagnosing liver fibrosis in children with CF determined that the APRI is superior to the AST/ALT ratio, FIB-4 score, GGT, GGT/platelet ratio, and platelet count, showing an AUROC of 0.90; 95%CI = 0.830-0.970; p = 0.0380. The same study indicated that the elevation of the APRI cutoff point of ≥ 0.425 has an odds ratio of 23.8 (95%CI = 5.2-109.7; p < 0.001) for CF-associated liver disease[15]. Liver biopsy was not performed in our patients, which is a deficiency to be considered in this study; however, other studies in children with CF have indicated that APRI is a good surrogate marker to establish the presence of liver fibrosis[16,17].

In the annual follow-up of children with CF, it is recommended that transaminases be evaluated and if alterations are found, hepatic ultrasound is initiated[18]. Partial or total hepatic hyperechogenicity is suggestive of steatosis and is the most common ultrasound finding in children with CF[19]. The patients included in this study were also evaluated by liver ultrasound, finding alteration of hepatic echogenicity in 39%; however, when comparing transaminases and other liver function tests, no difference was found, even though the percentage was lower in children with elevated transaminases. This is in contrast to other studies; abnormal echogenicity has been reported to precede biochemical or clinical evidence of liver disease. One study shows that two-thirds of children with abnormal hepatic echotexture and 50% with portal hypertension had no biochemical or clinical evidence of CF-associated liver disease at the time ultrasound changes were first observed[20]. It should be considered that ultrasound is an operator-dependent study and that there is intra- and interobserver variability in ultrasound images, and children with normal liver ultrasound may have advanced fibrosis, so a normal ultrasound does not exclude significant liver fibrosis[3]. A weakness of the study is that only biochemical tests of liver function and ultrasound were available, and ideally, elastography or other surrogate markers should be included for the evaluation of liver fibrosis and correlation tests should be performed to validate our findings.

Conclusion

In this study, we found that more than half of the children with CF at diagnosis may have elevated transaminases

and according to the APRI estimate, 30.5% may have liver fibrosis, also observing a good correlation of APRI with other liver function tests. In this study, we observed that liver ultrasound may be normal, even when there is biochemical evidence of liver disease.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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