



# Wilson's Disease and Cystic Fibrosis. An Infrequently Recognized Association

Daniela Andrea Sturla Álvarez<sup>1</sup>, Julio Alberto Vázquez Gómez<sup>1\*</sup>, Carolina Muñoz Codoceo<sup>2</sup>, Yurami Sánchez Santacruz<sup>3</sup>, Andrés Urquía Reinke<sup>4</sup>, José Ramón Villa Asensi<sup>5</sup>, Rosa Ana Muñoz Codoceo<sup>1</sup>

<sup>1</sup>Sección de Gastroenterología y Nutrición, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

<sup>2</sup>Servicio de Aparato Digestivo, Hospital 12 de Octubre, Madrid, Spain

<sup>3</sup>Servicio de Aparato Digestivo, Hospital Central de la Defensa Gómez Ulla, Madrid, Spain

<sup>4</sup>Servicio de Anatomía Patológica, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

<sup>5</sup>Sección de Neumología, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

## Abstract

"Cystic Fibrosis-Related Liver Disease" (CFLD) has a prevalence of 30% to 50% and is another consequence of CFTR dysfunction. Its spectrum can vary from an elevation of transaminases to cirrhosis with portal hypertension, constituting the second cause of death in these patients after pulmonary disease.

We present the case of two twin brothers diagnosed with CFLD with a torpid evolution of this complication. After searching for other liver diseases, they were diagnosed with Wilson's disease.

Although CFLD is a relatively common entity, it does not exclude that other concomitant processes may be associated. Wilson's disease is an autosomal recessive pathology in which there is an alteration of copper metabolism, depositing in the liver and frequently associating hepatic and neurological alterations.

In the literature, there is only one case like those described in this study, highlighting the importance of expanding the differential diagnosis when hepatic impairment is observed in CF patients.

**Keywords:** Cystic fibrosis-related liver disease; Wilson's disease; Hepatic impairment; Hepatic steatosis

## Introduction

Cystic Fibrosis (CF) is the most common, severe, autosomal recessive genetic disease in caucasians. The incidence is estimated to one for 5,000 live births [1]. CF is caused by mutation in the gene encoding a defective chloride channel in epithelial cells, named Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). This channel is present in several epithelial organs' surfaces, producing thick secretions which interfere with multiple organs' functions [2].

"Cystic Fibrosis-Related Liver Disease" (CFLD) appears in 30% to 50% of CF patients. Includes a wide range of hepatobiliary abnormalities: Mild hypertransaminasemia, focal biliary cirrhosis, multilobular cirrhosis, and portal hypertension. It represents the second cause of mortality in these patients (3.3% of mortality related to cystic fibrosis), after lung disease. The diagnostic criteria established by in 2011 is the most widely used in pediatrics, and is defined by the presence of two or more of the following: a) hepatomegaly and/or splenomegaly confirmed by ultrasound; b) elevated transaminases >1.5 to 2 times the Upper Limit of Normal (ULN), more than 6 months; c) ultrasound evidence: Parenchymal heterogeneity, nodularity or increased liver echogenicity or signs of portal hypertension; d) liver biopsy with focal biliary cirrhosis or multilobular cirrhosis [3-5].

Wilson's disease is an autosomal recessive, inherited disorder, in which defective biliary excretion of copper leads to its accumulation, particularly in the liver and brain. It is now recognized to be more common than previously thought, with a prevalence of 1 per 30,000 live births. Most of the symptomatic patients are between 5 to 35 years old. Wilson's disease occurs due to mutations of the ATP7B gene, which encodes a copper-transporting P-type ATPase, whose dysfunction results in the accumulation of copper in the hepatocyte and a decrease in ceruloplasmin synthesis. The diagnosis is made in patients with low ceruloplasmin, high 24-h copper urine excretion, and Kayser-Fleischer ring. Although there are other tests, necessary for the diagnosis, the next step usually is

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### \*Correspondence:

Julio Alberto Vázquez Gómez,  
Gastroenterology and Nutrition Section,  
Hospital Infantil Universitario Niño  
Jesús, Av. Menéndez Pelayo, 65,  
28009, Madrid, Spain,  
E-mail: julioalberto.vazquez@salud.  
madrid.org

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medium, provided the original work is  
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liver biopsy and/or genetic studies [6-8].

There is only one case reported, in the literature of Wilson's disease of a patient with concomitant Cystic Fibrosis [9].

## Clinical Case

Two twin brothers, who were product of *In Vitro* Fertilization (IVF) resulting in a dichorionic-diamniotic twin pregnancy, were born to a 32-year-old nulligravida *via* cesarean section at 33 weeks gestational age. Twin A: Male, 2130 gr, Apgar scores 9/9 at 1 and 5 min after birth, respectively, but goes on to develop symptom of RDS, requiring CPAP support. Twin B: Male, 1820 gr, Apgar score 9/9, healthy. Both were admitted to the Neonatology Unit for 14 days, due to prematurity, feeding difficulties and RDS in Twin A. The baby's first stool (meconium) was present in the first 24 h of life and begin enteral feeding by nasogastric tube the first day of life. Metabolic screening was not performed, because at that time, it was not included in newborn assessment protocol.

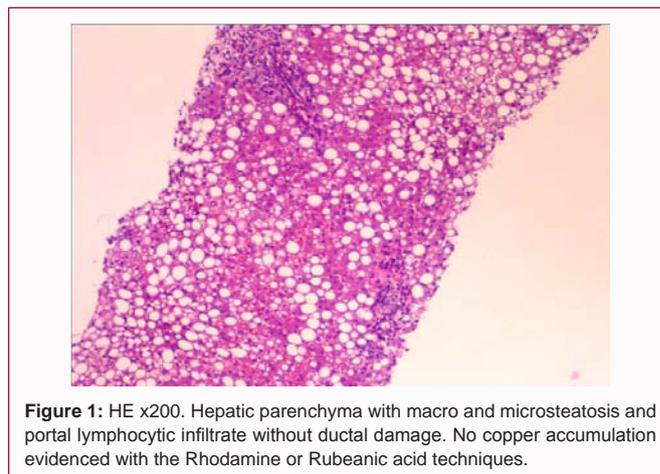
Twin A, at 4 and half months old (December 2006), required hospital admission due to hypoxemia and weight loss. A blood test showed: Hyponatremia, hyperkalemia, and hyperchloremia with a metabolic alkalosis. Sweat test was performed and resulted in 100 mEq/L. Due to the high suspicion for cystic fibrosis; the decision was made to run the same studies in Twin B, who had exhibited poor weight gain. His results were significant for hyponatremia, metabolic alkalosis, and sweat test was 98 mEq/L. A genetic study was carried out that confirmed the diagnosis, both cases with a homozygous F508del mutation.

After diagnosis, annual follow-up was carried out by Gastroenterology Unit, with complete physical examination, blood tests (liver evaluation), abdominal ultrasound, and starting in 2015, liver elastography control. At 3 years old (2009), they started weight based Ursodeoxycholic acid. Both twins were healthy exhibiting adequate nutritional status, with normal serial measurements of weight and height.

Twin A had normal ultrasounds until 2013, when he began to exhibit diffusely increased liver echogenicity, prompting the diagnosis of hepatic steatosis at last in 2016. Twin B also had normal ultrasound until 2016, when hepatic steatosis was also diagnosed. Annual liver elastography yielded a right hepatic lobe shear rate always below 1.27 meters/second (normal value). In 2018, both brothers were diagnosed CFLD, based on the presence of elevated transaminases (GOT, GPT and GGT). Liver enzymes showed partial improvement in successive controls, despite not making changes in the treatment with Ursodeoxycholic acid.

In January 2020, both were started on Symkevi® (Tezacaftor/Ivacaftor). After that, a progressive elevation of liver enzymes was observed again. Although drug induced liver injury is a known side effect of this treatment, we decided to stop the medication in August 2007. Liver injury kept getting worse, suggesting another etiology could be involved. The differential diagnosis was expanded as follows: Negative hepatotropic virus serologies (HAV, HBV, HCV, EBV, CMV, HIV) and Toxoplasma; normal alpha1-antitrypsin levels; negative autoimmune hepatitis test and celiac disease markers, normal iron profile, but ceruloplasmin levels were below the lower limit of normal (2.58 mg/dl and 2.2 mg/dl, in Twin A and Twin B, respectively).

Twenty-four-hours urine copper output measurements were



**Figure 1:** HE x200. Hepatic parenchyma with macro and microsteatosis and portal lymphocytic infiltrate without ductal damage. No copper accumulation evidenced with the Rhodamine or Rubeanic acid techniques.

collected, and in both cases, levels were twice the upper limit of normal (155.7 ug and 150.7 ug in 24 h, respectively). No detected Kayser-Fleischer ring, per Ophthalmology evaluation. We decided to perform a liver biopsy, which showed diffuse macro and microsteatosis, as well as lymphocytic infiltrates in portal spaces, no bile ducts alteration. The liver copper results were: 920 and 1316 mcg/g of liver tissue in Twin A and in Twin B, respectively. Additionally, a molecular study of the ATP7B gene was requested, detecting two heterozygosity pathogenic variants (c. 1934T>G; p. Met645Arg/c. 2304Dup; p. Met769Hisfs26), establishing the diagnosis of Wilson's disease (Figure 1).

## Discussion

CFLD is an important cause of mortality in patients with Cystic Fibrosis [2]. It is more frequently diagnosed in males, in those with severe genetic variability, and with pancreatic insufficiency, which were all characteristics of our two patients. When risk factors are present, close medical monitoring is crucial for early detection of the disease. In our patients, it was diagnosed according to the Debray et al. [2] criteria. Both patients had been receiving treatment with Ursodeoxycholic acid for years, which according to some studies, might have delayed the development of the disease. Despite no changes in treatment, the patients showed progressive improvement in laboratory abnormalities. However, years later, patients worsened again, and when drug induced hepatotoxicity from Symkevi® was ruled out, the diagnosis of Wilson's disease was established. There is only one case of Wilson's disease in a patient with CFLD in the literature [9].

Some studies had suggested that Ursodeoxycholic acid delays the development and progression of CFLD. In 2017, the Cochrane carried out a systematic review in this regard, concluding: Current available evidence is insufficient to justify routine use in these patients [10].

Both disorders are rare genetic diseases, hence why there are no studies of Wilson's disease in patients with cystic fibrosis; with our report, there are only 3 clinical cases in the literature. However, if we estimate it according to the prevalence of the two diseases separately, the possibility of suffering both would be one in about 150 million live newborns. Despite this fact, if CFLD has a torpid evolution, we must suspect other causes of liver disease, Wilson's disease being one of them [1,6].

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