Case Report
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Severe and Early Hepatic Failure in A Neonate: A New CFTR Mutation Associated with Medium-Chain Acyl-CoA Deficiency

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ABSTRACT

We report a case of an infant who presented at one month of age with severe malnutrition and neonatal cholestasis. He was born at term in Romania where no cystic fibrosis screening was performed. He rapidly developed cirrhosis and portal hypertension associated with severe pulmonary involvement leading to death at six months of age. Cystic fibrosis was diagnosed based on sweat test and genetic exam. Molecular analysis for CFTR gene identified a new undescribed c.1853_1863del deletion and a SERPINA 1 mutation corresponding to PiS phenotype. Concomitantly, we evidenced medium-chain acyl-CoA deficiency (MCAD). To our knowledge, this association was never described and might be responsible for rapid clinical deterioration and early hepatobiliary complications.

Keywords: *Cystic Fibrosis, SERPINA 1 Mutation, MCAD, Neonate, Hepatic Failure, CFTR Gene*

Introduction

Failure to thrive was an usual presentation of cystic fibrosis (CF) diagnosis before implementation of newborn screening. However, cystic fibrosis-related liver disease (CFLD) is rarely present at birth, but increases by approximately 1% every year, reaching approximately 10% by age 10 and 32.2% (95% CI, 29.7-35.2) by age 25 (Boëlle *et al*., 2019). The CFTR genotype strongly influences the pancreatic insufficiency (Boëlle *et al*., 2019), but no genotype-phenotype correlation exists so far for CFLD. It is therefore likely that other hepatic chronic conditions, such as liver toxic environment, and intracellular hepatic injuries play a role in the early appearance of CFLD in CF patients. Despite the possible cumulative risk for severe disease liver disease, and the frequent use of genetic screening to find the cause of liver diseases in children, such an early and severe CFLD at this age was not found after extensive search in the literature.

Case Presentation

A one-month-old boy presented to our emergency department with severe malnutrition and a history of vomiting, diarrhea and weight loss. He was born in Romania of healthy suspected consanguineous parents. No neonatal CF screening was routinely performed in this country at that time. His birth weight at 37 gestational weeks was 2500 grams. Upon admission, a clinical examination revealed a dehydrated neonate with jaundice and acholic stools. His liver was tender and palpable four cm below the right costal margin. Liver function tests were abnormal, indicating cholestasis, without evidence of liver failure. Ultrasonography of the abdomen revealed a small gallbladder and a hyperechogeneous liver. Serology tests for hepatitis A and B, human immunodeficiency virus (HIV), toxoplasmosis, herpes simplex virus (HSV), cytomegalovirus (CMV), treponema pallidum and rubeola were negative. A cholangiography showed normal intrahepatic and extrahepatic bile ducts, thereby excluding biliary atresia. On the liver biopsy performed at one month of age there was a portal tract edema with mild periportal fibrosis, interlobular bile duct dystrophy and ductular reaction together with severe cholestasis and thick lamellated pale to yellow-orange inspissated bile in neoductules (Fig. 1A and 1B).

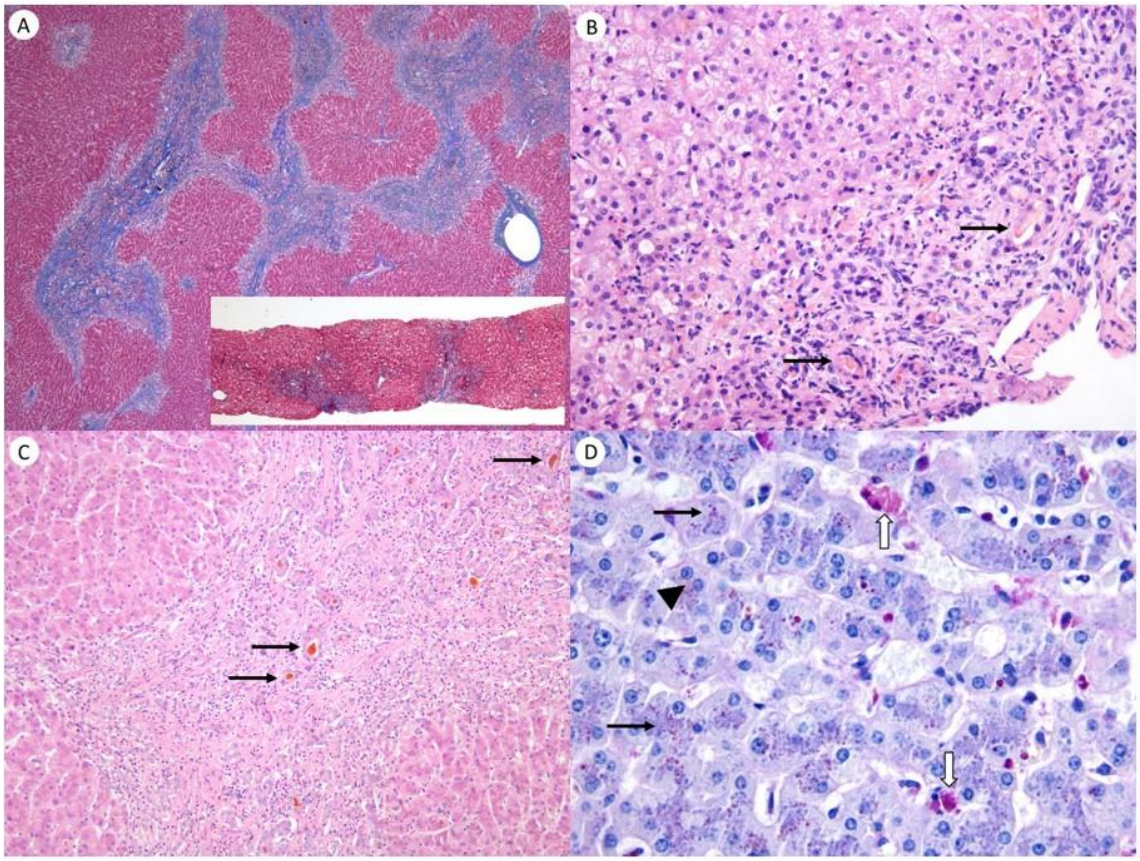

Figure 1: Histology of the liver, from the initial biopsy performed at one month of age (A, B), and from the necropsy (C, D), at seven months of age.

A: The initial biopsy (inset) showed portal tract edema, with mild periportal fibrosis (Masson's trichrome, original magnification x40 liver biopsy,). **B:** The liver biopsy was remarkable for pale, yellow-orange inspissated bile (arrows) (Hematoxylin&Eosin, H&E, x200). **C:** At necropsy, extensive fibrosis with ductular reaction, bile duct proliferation, cholestasis and thick inspissated bile were obvious (arrows) (Hematoxylin&Eosin, H&E, x100). **D:** Small PAS-positive, diastase-resistant hyaline globules were seen in a minority of the hepatocytes in the liver at necropsy only (arrows), a finding consistent with the observation that these globules are often not apparent in the first few months of age. Hepatocytes also showed cholestasis, with accumulation of bile within the cytoplasm (arrowhead). Ceroid pigment-laden Kupffer cells are also seen (white arrows) (PAS-diastase, x400).

At age six weeks, the Swiss newborn blood screening test was consistent with medium-chain acyl-CoA deficiency (MCAD), a diagnosis further confirmed by plasma acylcarnitine and urinary organic acid profiles. A homozygous mutation in the ACADM gene: c.985A>G, p. (Lys304Glu) was found. The feeding formula was enriched in medium chain triacylglycerol (MCT), and the avoidance of prolonged fasting episodes was recommended (Merritt and Chang, 2019). However, despite following this diet given for the whole time, there was progressive clinical and hepatic deterioration with persistent failure to thrive. In addition, the presence of pale inspissated bile in the liver biopsy prompted us to perform new exams.

Fecal pancreatic elastase was undetectable. Therefore, in spite of a normal immunoreactive trypsinogen (IRT) in the Guthrie test (but performed at six weeks of age because, the sweat test undertaken at three months of age was positive with a chloride level of 88mmol/L). Molecular analysis for the CFTR gene identified a new undescribed homozygous c.1853_1863del deletion. Both results confirmed the diagnosis of cystic fibrosis (CF). The child was started on pancreatic enzymes and liposoluble vitamins.

The severity of the liver disease and the pale-appearing bile were a further indication to conduct a SERPINA1 gene analysis, where a homozygous p.Glu288Val mutation was found with a PI*S phenotype.

Persistent absence of weight gain was observed during the following four months, despite close follow-up and effective management with adequate enteral and then parenteral nutrition. Portal hypertension with ascites, hypersplenism with associated pancytopenia, and a right chylothorax developed. The indication for liver transplantation was discussed as an option.

There was no history of respiratory symptoms until four months of age. The child then developed progressive respiratory deterioration with recurrent severe pulmonary infections due to Pseudomonas Aeruginosa and methicillin-sensitive Staphylococcus aureus (MSSA), leading to respiratory failure requiring mechanical ventilation at the age of six months. The patient deceased one month thereafter due to severe hepatic and respiratory failure. Postmortem examination showed severe lung and pancreatic lesions consistent with CF. The lungs showed severe acute bronchitis, bronchiolitis, bronchopneumonia,

and hypertrophied peribronchial mucoid glands with thick mucus. The pancreas showed severe exocrine atrophy, with ducts dilated by a thick PAS (Periodic Acid Schiff)-positive material, and thick adherent PAS-positive mucus was seen in the small intestine. The liver showed extensive and heterogeneous fibrosis. The presence of PAS positive globules (Fig. 1D) was compatible with the accumulation in the endoplasmic reticulum of non degraded proteins as seen in alpha 1 antitrypsine deficiency

Discussion

To our knowledge, this is the first report of a pathogenic c.1853_1863del deletion in CF. This novel mutation is not reported neither in the « Cystic Fibrosis Mutation Database » (CF Genetic Analysis Consortium http://www.genet.sickkids.on.ca/cftr/) nor in the « Human Gene Mutation Database » (http://www.hgmd.org/). This mutation probably represents a class I CF mutation, since the deletion of eleven nucleotides in the CFTR gene leads to a premature stop in CFTR translation. Clinical evolution was atypical for CF. The patient presented with early and rapidly evolving hepatobiliary complications leading to cirrhosis and portal hypertension in less than one year, prior to the development of major respiratory symptoms. Hepatobiliary complications in CF vary notably Neonatal cholestasis is a rare but possible presentation mimicking biliary atresia. Cholestasis resolves in the majority of cases within the first few months of life. When present, the natural progression of the hepatic disease is usually slow; liver failure and portal hypertension are described as late events, mostly after 10 years of age (Debray *et al*., 2017; Leeuwen *et al*., 2014). When severe, hepatic involvement is usually related to the more severe genotypes of CF, due to class I-III mutations (Rowntree and Harris, 2003). Several factors are associated with cystic fibrosis-related liver disease, including male gender (Leeuwen *et al*., 2014; Stonebraker *et al*., 2016), a history of meconium ileus, and pancreatic insufficiency (Leeuwen *et al*., 2014). The present case had two of the three listed risk factors, since there was no history of meconium ileus. Our patient developed early portal hypertension and severe pulmonary infections at approximately five months of age. The severe and early portal hypertension, despite adequate management (albumin infusions, diuretics, and nutritional support with enteral and parenteral nutrition), favoured the development of exudative enteropathy, chylothorax and refractory ascites. Susceptibility to early and severe respiratory infections was also potentially increased, secondary to the loss of immunoglobulins and lymphocytes in the digestive tract (Nagra and Dang, 2021). Portal hypertension could be an indication for liver transplantation because of life threatening haemorrhagic events in CF patients (Bartlett *et al*., 2009; Debray *et al*., 2017; Leeuwen *et al*., 2014; Stonebraker *et al*., 2016). It can also be hypothesized that the concurrent SERPINA1 gene mutation found in the patient, played a role in the severity of the liver fibrosis, possibly acting as a «modifier gene» (Bartlett *et al*., 2009). It is yet unclear whether the MCAD gene mutation under a controlled diet may also display such a modifier effect.

Conclusion

In conclusion, diagnosis of cystic fibrosis should always be considered in infants who present with failure to thrive and neonatal cholestasis (after excluding biliary atresia). The discovery of the c.1853_1863del mutation should suggest hepatobiliary complications, that are a major cause of morbidity and mortality and should be followed by rapid and optimal management. According to the literature, the association of MCAD deficiency and CF has never been reported previously. However, the identification of two different homozygous and recessive pathologies is not unusual in the context of consanguinity. Although the contribution of both the MCAD deficiency and of the PI*S phenotype in the severity and unusually rapid evolution of the liver disease remains hypothetical, we suspect that this association contributed to the severity of the clinical picture.

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