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CASE REPORT

Massive hepatomegaly with jaundice as a main presenting feature of cystic Fibrosis

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Abstract:
Cystic fibrosis (CF) is a recessively inherited disease caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. Patients classically present with evidence of pulmonary disease, malabsorption secondary to pancreatic insufficiency and high sweet chloride concentration. CF has can also be associated with a veriable phenotype which remains a diagnostic challenge. We report a case of a 2 year old girl with CF who initially presented with massive hepatomegaly and jaundice and was firstly suspected of a liver tumor. There was no personal or family history suggestive for CF. The diagnosis of CF liver disease was made after the results of the liver biopsy, sweat test analysis and confirmed with the existence of pathogenic mutation in the CFTR gene. Hepatomegaly and steatosis are known complications of CF but very uncommon as presenting features that lead to the diagnosis of CF. This report emphasizes the difficulty and importance of diagnosing cystic fibrosis in unusual patients.

Keywords: *hepatomegaly, steatosis, jaundice, CF liver disease*

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Introduction

Cystic fibrosis (CF) is a multi-organ genetic disease affecting 1 in 2500-3500 newborns worldwide. The disease is caused by mutations in the CTFR gene, located on chromosome 7 (7q31). CFTR functions principally as a cAMP-induced chloride channel and is responsible for the normal passage of chloride at the luminal surface of epithelial cells. The most common CFTR defect is the ΔF508 mutation, occurring in about 70% of patients with CF. Up to date more than 1600 mutations in the CFTR gene have been described. The large tissue distribution of CFTR protein explains why cystic fibrosis may affect multiple organs. The penotypic expression of the disease is extremely heterogeneous in terms of severity and type of organs involved [1].

The most common targets are the respiratory tract, the pancreas, and the digestive tract. Liver involvement in cystic fibrosis is much less frequent than both pulmonary and pancreatic diseases that are present in 80-90% of CF patients; liver disease affects only one third of CF patients [2]. Steatosis is the most common hepatic lesion in CF patients often found in asymptomatic patients. Sometimes it becomes severe and cause massive hepatomegaly.

In the literature there are only few reports of massive hepatomegaly as a presenting feature of cystic fibrosis. We

present a child with CF who presented with massive hepatomegaly and jaundice and firstly assumed as a liver tumour.

Case report

A-2-year old girl was referred to our hospital because of jaundice and massive hepatomegaly. The girl was third child of healthy non-consanguineous parents, born out of normal pregnancy and delivery with birth weight of 3,1 kg. Her perinatal course was completely normal and jaundice free. She was breastfed only in the first month and after that infant milk formula was induced. In the last 5-6 months the child had decreased appetite, and was fed mainly with chocolate wheat flakes, milk, and fruit juices. She had suffered from frequent respiratory infections, mainly concerning the upper respiratory tract that were never microbiologically investigated but treated with wide spectrum antibiotics. There were no previous hospital admissions. The family history for malignancies and genetic disorders was negative.

The girl became jaundiced four days before admission, and during examination by primary pediatrician and infectologist massive hepatomegaly was noticed. After excluding viral hepatitis she was referred to our Hospital for evaluation of a possible liver tumor.

On the physical examination at admission the girl looked seriously ill, febrile and icteric. Her weight was under the 3-rd percentile and her height on the 3-rd percentile for age. Chest examination revealed wide spread crackles and wheezing. Assessment of the abdomen was remarkable for hepatomegaly of 10 cm below the right costal margin. Physically there were no signs of congestive heart failure.

Laboratory results revealed iron deficiency anemia in the hemogram with hemoglobin value of 93g/l, red blood cells 3.3 x 10^{12}/l and serum iron level of 6.6 µmol/l. The leucocytes were 13.7 x 10^{9}/l, erythrocyte sedimentation rate 67 and C-reactive protein 42.4 mg/l pointing out an inflammatory process. There was remarkable hypokalemia with potassium value of 2.9 mmol/l, other electrolytes were within normal limits. The acid base status showed uncompensated metabolic alkalosis with pH value of 7.498; concentration of HCO_3 33.1 mmol/l, hypoxemia pO_2 of 7.77 kPa, and pCO_2 5.82 kPa. Serum kreatinine and BUN were normal. The total bilirubin was 94 µmol/L; conjugated bilirubin, 55 µmol/L and the serum transaminase levels were AST 93 U/L, ALT 41 U/L and γGT 123 U/l. The prothrombin time (PT) was 51 s (normal <13 s) and partial tromboplastin time 71 s (normal < 33s). These coagulation disturbances were completely normalized after parenteral vitamin K administration. Other biochemistry analysis showed hypoproteinemia and hypoalbuminemia with values of 54 and 23 g/l respectively. The immunoglobulins were within normal limits for the age. α fetoproteine level was normal, as well as levels for α-1-antitrypsin, ceruloplasmine and antibodies for autoimmune hepatitis type 1 and type 2. Rapid screening test for tissue transglutaminase IgA antibodies was negative. Metabolic work-up showed normal values of aminoacides in serum and urine and normal organic acids in urine. Free carnitine concentration and acylcarnitines messured by tandem mass spectrometry were all within normal limits.

Sweat test was positive with chloride concentration of 110 mmol/l performed at two separate occasions. Abdominal ultrasound showed hepatomegaly with hyperechogenicity without any focal defects of the parenchyma, and the abdominal CT large liver filling almost whole left hemiabdomen with homogenously low density structure of the parenchyma interpreted as massive hepatic steatosis (Figure 1).

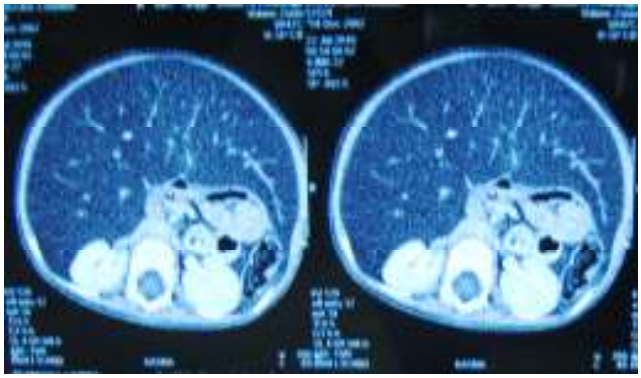

Figure 1. Abdominal CT showed enormous large liver with low density structure of the parenchyma interpreted as massive hepatic steatosis

Liver biopsy was performed and histological assessment of the liver biopsy revealed massive macrovesicular steatosis present in 80% of hepatocytes and initial fibrosis.

Chest radiograph at admission showed consolidation in projection of the lingula of the left lung lobe. Tracheal aspirate was positive for *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Molecular analysis revealed homozygous state for ΔF 508 mutation. After three weeks treatment of pneumonia control chest X-ray was done which showed peripheral hyperinflation and peribronchial infiltrates, finding that corresponds of a pronounced CF lung disease. Long term treatment for lung disease was provided. The girl was also

treated with ursodeoxycholic acid, pancreatic enzymes (Creon), carnitine supplementation and adequate nutritional intake.

On the last ambulatory control at age of 3 years and 10 months the girl's body weight is on the 50th percentile and height on the 25th percentile for age. The hepatomegaly receded almost completely. Bilirubin level, transaminases, serum protein and albumin values were all within normal limits.

Discussion

Hepatobiliary abnormalities associated with cystic fibrosis vary in nature and range from defects attributable to the underlying genetic defect to those related to systemic disease and malnutrition. Because of the increased duration of survival in patients with CF the clinical attention to other manifestations of the disease has increased, particularly for the wide spectrum of hepatic problems.

Liver disease associated with CF usually develops before puberty, showing a progressive increase in prevalence with age, from 10% in infants to 72% in adults [2-3]. It is often asymptomatic and displays slowly progressive course. The most common presentation is the occasional finding of hepatomegaly on routine physical examination, which is often but not always associated with abnormalities of liver biochemistry. Jaundice is limited to patients with neonatal cholestasis and with end-stage multilobular biliary cirrhosis.[2] Although rarely, CF may present with a picture of neonatal cholestatic jaundice mimicking biliary atresia because of obstruction of extrahepatic bile ducts by viscous biliary secretions, as direct consequence of the basic CF defect, but generally resolves spontaneously within the first months of life without progression to clinically relevant LD [4]. Our patient had cholestatic jaundice and impairment of liver function tests.

Cystic fibrosis is known to be one of the possible etiologies of fatty liver disease in children. Steatosis has been reported in cystic fibrosis patients of any age, with prevalence figures ranging between 23% and 67%, but is massive in less than 5% of cases [5-6].

Massive steatosis was once frequently observed in newly diagnosed patients with pancreatic insufficiency and severe malnutrition, but has now become less frequent due to earlier diagnosis and appropriate nutritional care. As hepatocytes do not express CTFR, steatosis has been usually assumed to be of secondary, toxic, or nutritional origin often associated with nutritional deficiencies (e.g. of essential fatty acids, carnitine, choline minerals and trace elements) [7]. Thus, it has been considered as a benign condition, without proven

relationship to subsequent development of cirrhosis, but in a few patients steatosis was recognized as the first step in the progression of more severe hepatic lesions [3].

Literature search revealed only few reports of a hepatomegaly as the presenting feature of CF. Wilroy et al. [8]. in a case report described delayed diagnosis of cystic fibrosis in a 2 year old child with extensive fat replacement of the liver. Treem and Stanley [9] described massive hepatomegaly, steatosis and secondary plasma carnitine deficiency in an infant with cystic fibrosis. Its' massive hepatomegaly and steatosis developed during a severe viral respiratory illness and prolonged fasting, and disappeared after correction of metabolic abnormalities and institution of a high carnitine diet. However plasma carnitine concentration in our patient was normal.

Collardeau-Frachon et al. [10].described four cases of pediatric patients in whom the diagnosis of cystic fibrosis was made only after the histological examination of a liver specimen, recalling that the diagnosis of cystic fibrosis must be considered in children presenting with an unexplained liver disease.

Cystic fibrosis in our patient was presented in much unusual mode of presentation. There was no known prior personal or familial history of cystic fibrosis. Massive hepatomegaly and jaundice was the main clinical feature initially considered for a possible liver tumor or neoplasm. There was no evidence of viral infection or autoimmune disease or metabolic diseases ruled out by adequate biochemical tests. After the results of the liver biopsy, the positive sweat test and homozygous ΔF508 mutation the diagnosis of CF was made.

The child also manifested pulmonary symptoms that were never examined before. After nutritional supplementation and treatment with UDCA in our patient there was significant reduction in liver size and improvement in liver function tests.

In conclusion, we report an unusual pediatric case with massive hepatomegaly to underline the variety of clinical presentations which may be associated with cystic fibrosis. It is important that physicians are mindful of the wide spectrum of disease presentations and consider cystic fibrosis in clinical and laboratory evaluation of patients with liver diseases.

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