Wilson disease as a cause of liver injury in cystic fibrosis

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Abstract

Cystic fibrosis-related liver disease affects approximately one third of all patients with cystic fibrosis. Initial signs of other liver diseases including the genetically determined disorders of the liver co-inherited with cystic fibrosis may be obscured by or ascribed to cystic fibrosis-related liver disease. We report a patient shown to suffer simultaneously from cystic fibrosis and hepatic Wilson disease. Our case documents that in patients with cystic fibrosis presenting with liver disease, when unusual clinical and/or laboratory abnormalities appear and fail to respond to standard therapy, a second disease, including rare inherited metabolic disorders such as the hepatic form of Wilson disease or α1-antitrypsin deficiency, should be suspected.

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1. Introduction

Cystic fibrosis-related liver disease (CFLD) affects approximately one third of all patients with cystic fibrosis (CF, OMIM #219700), most severely as focal or multilobular liver cirrhosis associated with steatosis [1,2]. Cirrhosis is related to increased viscosity of bile and to injury or necrosis of biliary epithelia, arising from decreased function and/or aberrant expression of CFTR. That only some patients with CF develop CFLD, which varies greatly in severity even among patients with the same CFTR genotype, indicates that other factors influence its pathogenesis. Exogenous factors, concomitant events, and genetic modifiers for CFLD are listed elsewhere [1]. Initial signs of other liver diseases including the genetically determined disorders of the liver co-inherited with CF may be obscured by or ascribed to CFLD. Here we report, to our best knowledge, the first patient shown to suffer simultaneously from both CF and Wilson disease (WD; OMIM #277900), a rare autosomal-recessive disorder characterized by hepatic accumulation of intracellular copper resulting in progressive liver disease, and neurological abnormalities.

2. Case report

The patient, of Caucasian origin (Czech), was born to healthy non-consanguineous parents at 31 weeks of gestation. He suffered from meconium ileus which was treated with temporary ileostomy. CF was suspected. The mean sweat chloride concentration was 98 mmol/L. Homozygosity for the prevalent mutation F508del was found by screening of CFTR (Fig. 1A). Sino-pulmonary and pancreatic disease developed during the first year of life. Liver disease (LD), considered to be CFLD, was first manifest at age 5 years, after appendectomy, as elevation of serum liver enzyme activities (Table 1) with hepatomegaly and mildly increased hepatic echogenicity on ultrasound examination. As no signs of hemolysis were present, mild unconjugated hyperbilirubinemia was ascribed to Gilbert syndrome (OMIM #143500), confirmed by genotyping of the UGT1A1 promoter (Fig. 1B). Ursodeoxycholic acid was started...
Liver enzyme activities decreased after 3 months (Table 1) but began again to rise at age 7 years despite continuous administration of ursodeoxycholic acid.

At age 9 years the patient was hospitalized with anorexia and markedly abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) values (Table 1). Height was within 0.1 SD of normal range and body mass index was 14.4 (−1 SD). Hepatomegaly, splenomegaly and signs of portal hypertension were not found. Values for albumin, cholesterol, plasma cholinesterase, α-fetoprotein, α1-antitrypsin, prothrombin time and immunoglobulins were within the normal range. Autoantibodies (ANA, ANCA, ASMA, LKM, AMA, dsDNA, ENA and SLA) were not detected. Serologic evidence for hepatotropic-virus infection (HAV, HBV, HCV, EBV, CMV and HSV) was not found. The gallbladder and extrahepatic bile ducts were sonographically normal and without gallstones.

Serum values for copper and ceruloplasmin were repeatedly far below the normal range (Table 1). Urinary output of copper was marginally elevated and rose to 1422 µg/24 h with formal D-penicillamine challenge according to Roberts and Schilsky [3] (500 mg of D-penicillamine at the beginning and again 12 h later during 24-hour urine collection, evidence for WD N1600 µg/24 h). Kayser–Fleischer rings were not present.

Findings on neurologic examination were normal. Quantitative analysis of copper in a liver biopsy specimen (1450 µg/g dry weight, normal ≤50 µg/g) confirmed hepatic WD. The liver biopsy specimen was too small for both copper quantification and histologic study.

Molecular genetic analysis of all exons of ATP7B together with their adjacent intronic regions disclosed the known missense mutation c.2930C>T (p.T977M) in exon 13 [4] (Fig. 1C), confirmed present in the mother as well. However, a second mutated allele in trans was not found on sequencing of both patients’ DNA strands. Complex intragenic rearrangements were not detected by multiplex ligation-dependent probe amplification (MRC-Holland™, Amsterdam, The Netherlands).

D-penicillamine and pyridoxine were begun. Clinical-biochemistry abnormalities resolved gradually, reaching almost normal values after 18 months of treatment. Thirty months after initiation of D-penicillamine therapy, body mass index had increased to 17.2 (~0.4 SD), urinary copper excretion dropped to 508 µg/24 h while receiving D-penicillamine at maintenance dose and clinical-biochemistry indices of hepatobiliary injury remained normal, except for bilirubin and ALT values (Table 1).
3. Discussion

The primary aim of clinical and laboratory screening for CFLD is early diagnosis during an asymptomatic phase. Screening is particularly important in patients at increased risk of CFLD conferred by male sex, meconium ileus, and pancreatic insufficiency, as well as by the “severe” pancreatic CFTR genotype with Class I–III alleles in homozygous or compound heterozygous state. In our patient, mild clinical-biochemistry abnormalities led to the diagnosis of CFLD, supported by improvement in laboratory parameters within 3 months after ursodeoxycholic acid therapy began. Unexpected recurrence of laboratory signs of hepatobiliary disease suggested an intercurrent event and/or a co-inherited genetic disease. The final diagnosis of simultaneously present WD was supported by decreased serum ceruloplasmin concentrations, urinary copper excretion with formal penicillamine challenge exceeding 5× the upper limit of normal value [5], increased hepatic copper concentration, presence of a mutation in ATP7B and a clinical response to D-penicillamine treatment. The result of penicillamine challenge test interpreted using the cutoff limit of 1600 µg/24 h [3] was marginal, however, still compatible with WD [6].

As WD is an autosomal-recessive disorder, heterozygotes with a single ATP7B mutation should be unaffected. Molecular genetic investigation performed in our patient revealed only one pathogenic ATP7B allele: although the detected c.2930C>T ATP7B mutation is rare in Czech patients [7], it is the second most common mutated ATP7B allele in Sweden [4] and its pathogenic potential is undisputable. A single ATP7B gene mutation, or none, was found in 27.5% of 200 unrelated WD patients of Czech or Slovak origin reported by Vrábelová et al. [7]. Therefore we cannot definitively state that another mutation in trans is not located within promoter or intronic sequences of ATP7B that were not examined. Nonetheless, we believe that WD in our patient most likely resulted from compound heterozygosity at ATP7B, since the mother transmitting mutated alleles of both ATP7B and CFTR genes is asymptomatic and her serum levels of copper and ceruloplasmin and urinary output of copper were normal.

The contribution of CF to LD was scant at worst in our patient. The child has never been severely cholestatic, no abnormalities of bile ducts were found by repeated ultrasonography and the copper content of liver tissue was within the range typical for paediatric WD. This does not mean, however, that cholestasis or chronic liver injury caused by CF cannot promote manifestation or worsen the course of simultaneously present WD. Early diagnosis of WD is of particular importance because acute liver failure can be prevented by specific therapy.

We conclude that in patients with CF presenting with LD, when unusual clinical and/or laboratory abnormalities appear and fail to respond to standard therapy, a second disease, including rare inherited metabolic disorders such as α1-antitrypsin deficiency [8] or the hepatic form of WD (this observation), should be suspected.

Conflict of interest statement

The authors have no conflict of interest that could influence the content or processing of this manuscript.

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References