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Autosomal dominant polycystic liver disease in a family without polycystic kidney disease associated with a novel missense protein kinase C substrate 80K-H mutation

Ramón Peces, Joost PH Drenth, Rene HM te Morsche, Pedro González, Carlos Peces

INTRODUCTION

Proof of existence of autosomal dominant polycystic liver disease (ADPLD) as a distinct genetic entity, independently from autosomal dominant polycystic kidney disease (ADPKD), stems from three studies in which isolated familial polycystic liver disease (PLD) was shown to be unlinked to the PKD1 or PKD2 loci[1-3]. In 2000, Reynolds et al[4] identified a locus for ADPLD on chromosome 19p13.2-13.1. In 2003, two independent groups demonstrated that mutations in PRKCSH, encoding the β-subunit of glucosidase II, a N-linked glycan-processing enzyme in the endoplasmic reticulum, cause isolated ADPLD[5,6]. Given its role in the pathogenesis of ADPLD, this protein has been renamed as hepatocystin[7]. Very recently, Davila et al[7] found that mutations in SEC63 (chromosome 6q21), encoding a component of the protein translocation machinery in the endoplasmic reticulum, also cause ADPLD. Mutations in PRKCSH and SEC63 probably account for less than one-third of ADPLD cases, indicating that there is at least one more locus associated with this disease[7].

We have reported here the first Spanish family with a severe form of ADPLD not associated with ADPKD. The proband manifested displacement of abdominal structures by a massively enlarged liver causing portal hypertension and inferior vena cava compression.

CASE REPORT

A 36-year-old woman presented with a long history of abdominal enlargement. She had two pregnancies and live births at 29 and 34 years of age, respectively. Physical examination showed a bulging abdomen with a palpable mass extending from the right hemiabdomen to the left quadrant reaching 10 cm below the umbilicus. Laboratory data showed 0.9 mg/dL creatinine (normal range 0.6-1.2 mg/dL), 7.2 g/dL total proteins (normal range 6.8-7.4 g/dL), 137 mg/dL total cholesterol (normal range 140-220 mg/dL), 30 mg/dL triglycerides (normal range 50-128 mg/dL), 29 IU/L aspartate transaminase, 29 IU/L alanine transaminase and a total bilirubin of 1.2 mg/dL (normal range 0.2-1.2 mg/dL).

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Abstract

Polycystic liver disease (PLD) is characterized by the presence of multiple bile duct-derived epithelial cysts scattered in the liver parenchyma. PLD can manifest itself from PLD associated with ADPKD, although it may have similar pathogenesis and clinical manifestations. Recently, mutations in two causative genes for ADPLD, isolated ADPLD and ADPKD, have been identified. We report here a family (a mother and her daughter) with a severe form of ADPLD not associated with ADPKD produced by a novel missense protein kinase C substrate 80K-H (PRKCSH) mutation (R281W). This mutation causes a severe phenotype, since the two affected subjects manifested signs of portal hypertension. Doppler sonography, computed tomography (CT) and magnetic resonance (MR) imaging are effective in documenting the underlying lesions in a non-invasive way.

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Key words: ADPLD; Hepatic cysts; Hepatocystin; Inferior vena cava compression; Polycystic liver disease; Portal hypertension

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12-16 g/dL), 66.6 fL MCV (80-100 fL), 21.8 pg MCH (normal range 26-34 pg), 5.9% hemoglobin A2 (normal range 2-3.5%), 3 500/μL white blood cell with normal differentiation, 105 000/mm³ platelet count, 0.6 mg/dL creatinine, 6.9 g/dL total proteins, 177 mg/dL total cholesterol, 101 mg/dL triglycerides, 31 IU/L aspartate aminotransferase, 19 IU/L alanine aminotransferase, 14 IU/L gamma glutamyl transpeptidase, 109 IU/L alkaline phosphatase, 2.1 mg/dL total bilirubin, 79% prothrombin time and 362 mg/dL fibrinogen. Ultrasonography and CT of the abdomen demonstrated PLD. There were signs of portal hypertension with varices in the hepatic hilum, gastrohepatic ligament, and lower esophagus. The spleen was enlarged, measuring 17.6 cm in length. The kidneys were normal. The patient was healthy and had no variceal bleeding. She refused any invasive procedure.

DNA sequencing and mutation detection
DNA was isolated from peripheral blood leukocytes by standard procedures. We performed polymerase chain reaction amplification using specific primer sets for all the 18 exons that constitute the open reading frame of PRKCSH. We determined the nucleotide sequences of the amplified fragments by fluorescence sequencing with dye-terminator chemistry on an ABI3700 capillary sequencer (Perkin-Elmer Applied Biosystems).

RESULTS
Sequence analysis of PRKCSH gene from DNA isolated from the proband demonstrated a base pair change (C>T) on one allele at position 841 (Figure 3). This mutation, C841T which is predicted to change the amino acid composition of hepatocystin, changes arginine to tryptophan at codon 281 (R281W).

Figure 1 Massive polycystic liver disease on coronal MR imaging (A), caudal and posterior displacement of abdominal organs by the massively enlarged liver on sagittal MR imaging (B), and compression of the inferior vena cava (arrow) produced by the massively enlarged liver (C) on MR angiograph.

Figure 2 Family pedigree of the patient.

Figure 3 Sequence identification of the C>T changes in exon 10. This mutation, C841T which is predicted to change the amino acid composition of hepatocystin, changes arginine to tryptophan at codon 281 (R281W).
reticulum membrane, a low-density lipoprotein receptor domain class A (LDLa) domain, two EF-hand domains, a glutamic-acid-rich region, a mannose-6-phosphate receptor domain and a conserved C-terminal HDEL amino acid sequence for endoplasmic reticulum retention. Hepatocystin is an endoplasmic reticulum-resident enzyme that is involved in carbohydrate processing and quality control of newly synthesized glycoproteins.

DISCUSSION

ADPLD is a rare autosomal dominant disorder that has been described in fewer than 50 families from Finnish, Dutch, American, Belgian, and Spanish-Belgian ancestry. The pathology of ADPLD consists of numerous cysts of biliary epithelial origin spread throughout the liver parenchyma. This disease is distinct from ADPKD1 and ADPKD2, in which affected individuals develop bilateral renal cysts and liver and pancreatic cysts in advanced cases. Cystic liver disease occurs in a substantial portion of patients with ADPKD and end-stage renal disease. Factors influencing the prevalence of PLD in ADPKD include female sex, age (prevalence of PLD is 10% in the third decade, but 60% in patients older than 60 years), and pregnancy (multiparity is associated with increased size and number of cysts in ADPKD).

The recent cloning of the gene involved in ADPLD has greatly facilitated the possibility of a firm molecular diagnosis in our family. Up to now, a total of nine different PRKCSH mutations have been described. We detected a novel missense PRKCSH mutation (R281W) in our family. Several lines of evidence suggest that the R281W represents a bona fide disease causing mutation. First, there is segregation of the mutation with the disease in our family. Second, arginine, a positively charged amino acid is replaced by tryptophan which is neutral. Lastly, the C at position 841 is highly conserved among the species.

Table 1 Missense PRKCSH mutation detected in our family

<table>
<thead>
<tr>
<th>Species</th>
<th>Asp</th>
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<td>RN</td>
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<td>A</td>
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<tr>
<td>Patients</td>
<td>G</td>
<td>A</td>
<td>A</td>
<td>G</td>
</tr>
</tbody>
</table>

HS: Homo sapiens; BT: Bos Taurus; MM: Mus musculus, RN: Rattus norvegicus. The missense PRKCSH mutation detected in this study is indicated in bold, and for comparison the corresponding nucleotides from various species are included. The numbers on top correspond with the codon numbering of hepatocystin, while Asp is aspartic acid; Lys is lysine; Tyr is tyrosine; Arg is arginine. Note that the C at position 841 is highly conserved among the species.

bile duct cells that have undergone somatic second hits. However, the two-hit model has not been investigated in isolated PLD.

The clinical profile of PLD has been defined by Qian et al. who on the basis of a small series concluded that extra hepatic manifestations are infrequent but may include simple renal cysts, intracranial aneurysms, and mitral valve abnormalities. Genotype-phenotype relations remain speculative at this point. Liver cysts are usually asymptomatic, and as a consequence, the disease may go undetected and is likely to be underdiagnosed in the general population. Symptoms occurred are caused by the mass effect of the cysts, or the development of complications such as hemorrhage, infection, or rupture of cysts. Symptoms caused by the mass effect of the cysts include vague abdominal distension, early satiety, dyspnea, and back pain. Rarely, ascites can form because of hepatic venous outflow obstruction by cysts. Lower extremity edema is secondary to extrinsic compression of the inferior vena cava, hepatic veins, or portal vein by large or by many small or medium size hepatic cysts. Compression of the bile ducts can cause jaundice. The symptoms of compression or thrombosis of the inferior vena cava may be obscure and a high index of suspicion is required for the diagnosis. Liver metabolic and synthetic functions remain normal, although an increase in serum levels of alkaline phosphatase, bilirubin and gamma glutamyl transpeptidase, and a decrease in serum levels of total cholesterol and triglycerides have been described in some cases. The factors that affect disease progression are unclear. However, some risk factors for the progression of the disease are age, sex, number of pregnancies, and use of estrogen.

The proband manifested a massively enlarged liver, which caused abdominal heaviness and progressive hemodynamic changes. She presented displacement of abdominal structures by the massively enlarged liver and hepatic cysts not only caused extrinsic compression of the inferior vena cava, but also were responsible for portal hypertension. Whereas laboratory studies in the proband disclosed a slight increase in the serum levels of alkaline phosphatase and gamma glutamyl transpeptidase, and a decrease in serum levels of total cholesterol and triglycerides, the proband’s mother presented thrombocytopenia and a slight increase in total bilirubin.
As the proband's history shows, the disease may become highly symptomatic in young women. The more severe extensive development of the condition in the proband than in her affected mother contrasts with the reported greater severity of the liver involvement with age. The increased severity of the disease in the proband could be in relation, at least in part, with repeated pregnancies in this patient. However, other possible factors for the progression of the disease remain unknown. Screening of the at-risk members of the families of other affected patients could help to answer this question.

The presence of (few) renal cysts, as demonstrated in our proband who had 2 renal cysts does not preclude the diagnosis ADPLD. This is in accord with the data from another study that demonstrated PRKCSH mutations in four patients with polycystic livers who possessed at least one renal cyst. Most patients with PLD require no treatment. In highly symptomatic patients, percutaneous cyst aspiration, resection of the lobes of their livers for decompression may be indicated.

ACKNOWLEDGMENTS

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