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Case Report
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Rotor Syndrome: An Important Diagnosis to Make

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Abstract

A heightened awareness of the rare, yet benign, forms of hyperbilirubinemia is essential when dealing with hepatobiliary disorders. Rotor syndrome, as well as Dubin-Johnson syndrome, can be mistaken for more severe forms of hepatobiliary disease, which can lead to unnecessary and invasive therapeutic interventions with potential risk of complications. We herein present a case of a patient with Rotor syndrome whose misdiagnosis led to multiple risky interventions. Additionally, we discuss the important diagnostic tools used to identify Rotor syndrome and differentiate it from Dubin-Johnson syndrome.

Introduction

Rotor syndrome is a rare, benign and inherited cause of hyperbilirubinemia, which is often misdiagnosed as a more severe form of hepatobiliary disease. The identification of Rotor syndrome is essential in order to prevent misdiagnosis, which can lead to unnecessary investigations and treatment placing the patient at an unwarranted risk of complications. We herein present a case of a 35-year-old male with multiple hospitalizations for "recurrent cholangitis" and repeated interventions with endoscopic retrograde cholangiopancreatography (ERCP) who was ultimately diagnosed with Rotor syndrome.

Case Presentation

A 35-year-old nonverbal male with a history of traumatic brain injury resulting from a motor vehicle accident eleven years ago presents to the hepatology clinic for evaluation of persistently elevated serum bilirubin levels. He initially presented to the hospital one and a half years ago with nausea, vomiting, fevers and hypotension consistent with septic shock. He had an elevated total bilirubin level of 3.8 mg/dL (64.98 μmol/L) with a direct bilirubin of 2.6 mg/dL (44.46 μmol/L, 68% of total bilirubin), with normal aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels. He was diagnosed with acute cholangitis in the setting of his fevers and elevated bilirubin levels and was treated with intravenous antibiotics. He was immediately taken for ERCP, which showed multiple gallstones in the gallbladder, a common bile duct diameter of 5mm, no biliary strictures and no filling defects on cholangiogram. A biliary sphincterotomy with balloon sweep was done without any biliary stones to be removed. The patient improved clinically on antibiotics with resolution of his fevers and hypotension, but his serum bilirubin remained elevated. Despite the persistent hyperbilirubinemia, he was discharged to a rehabilitation center. He re-presented with the same symptoms five months later and was found to have an infiltrate on chest X-ray consistent with pneumonia and a persistently elevated bilirubin but normal ALT, AST and ALP. He was started on antibiotics for both pneumonia and presumed cholangitis in the setting of elevated bilirubin levels. He underwent emergent placement of a percutaneous cholecystostomy tube for biliary drainage and was eventually discharged despite persistent hyperbilirubinemia. He then underwent elective cholecystectomy two months later for known gallstones and developed fevers eight days postoperatively. A Computed Tomography (CT) scan was normal without any biliary dilation. Another ERCP to rule out biliary leak and cholangitis was normal. Magnetic resonance cholangiopancreatography (MRCP) was pursued and completely normal. Despite the normal MRCP findings, an elective ERCP was pursued one month later due to persistently elevated bilirubin levels. An internal biliary stent was placed and removed three months after. His direct and total bilirubin levels remained elevated and he was referred to the hepatology clinic for further assessment. At the hepatology clinic, he was hemodynamically stable without any symptoms and had a benign abdominal examination. A family history was unobtainable since he was nonverbal and resided in a group home. He was not on any hepatotoxic medications. An evaluation for chronic liver disease revealed negative hepatitis serologies, anti-smooth muscle antibody, antinuclear antibody and antimitochondrial antibody as well as normal iron studies, lipase and immunoglobulin levels.

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Table 1: The Features of Rotor syndrome and Dubin-Johnson Syndrome.

Characteristics	Rotor Syndrome	Dubin-Johnson Syndrome	Reference
Genetic Mechanism	Mutation or deletion in *SLCO1B1* and *SLCO1B3* Disrupts OATP1B1 or OATP1B3 transporter proteins on sinusoidal membrane of hepatocytes	Mutation in MRP2 (chromosome 10q23-q24) halts maturation and causes mislocalization of protein	[2,6]
Pathological Mechanism	Defective hepatic storage of conjugated bilirubin and disrupted clearance of drug leading to potential toxicities	Deficiency in biliary transport of non-bile acid organic anions	[4]
Inheritance	Autosomal recessive	Autosomal recessive	
Urine Coproporphyrin	Increased total urine coproporphyrin (65% coproporphyrin I)	Normal total urine coproporphyrin (80% coproporphyrin I)	
Histology	Normal	Black liver with dark melanin-like pigment	
BSP clearance*	Delayed, with 50% reduction	No biliary transport	
Precipitants	OCP, pregnancy, other illness	OCP	

BSP: Bromopthalein Sodium; OCP: Oral Contraceptive Pill
*Test is no longer used in a clinical setting

Historic liver enzymes and bilirubin levels were obtained dating back to five years, which showed a chronic elevation in direct and total bilirubin levels with normal AST, ALT and ALP levels. Given his chronically elevated serum bilirubin with completely normal AST, ALT and ALP levels, Rotor or Dubin-Johnson Syndrome was suspected. A urine coproporphyrin excretion analysis exhibited an elevation in the total urine coproporphyrin level of 195.4 mcg/g creatinine (reference range: 23.3-32.4 mcg/g creatinine, SI: 297.4 nmol/24 hours) and an elevation in coproporphyrin I level of 171.5 mcg/g creatinine (reference range: 5.6-28.6 mcg/g creatinine, SI: 262.4 nmol/24 hours) consistent with a diagnosis of Rotor syndrome.

Discussion

Rotor syndrome is a rare, inherited, autosomal recessive disorder, which is benign and asymptomatic [1]. The diagnosis should be considered in any patient who has chronic mild non-hemolytic hyperbilirubinemia with normal AST, ALT, ALP, and gamma-glutamyl transferase (GGT) levels [1]. Rotor syndrome occurs due to a defect in the hepatic storage of conjugated bilirubin, which then leaks into the plasma leading to hyperbilirubinemia [1]. Studies have postulated the presence of homozygous mutations of transporter genes on chromosome 12 as the cause of this condition [2]. Rotor syndrome can be diagnosed by measuring urinary coproporhyrin excretion, which shows an elevation in the total urinary coproporphyrin level with 65 percent of the urinary porphyrins consisting of coproporphyrin I [1-4]. This test not only helps in the diagnosis, but also differentiates it from Dubin-Johnson syndrome, another rare cause of benign hyperbilirubinemia [1,4]. Differentiating Rotor syndrome from Dubin-Johnson syndrome is a key step in its diagnostic algorithm. Table 1 describes the differentiating features between Rotor syndrome and Dubin-Johnson syndrome. In Rotor syndrome, HIDA scan shows decreased uptake in the liver with prominent renal excretion [2]. Although liver biopsy is not required in the diagnosis, the absence of dark melanin-like pigments helps differentiate it from Dubin-Johnson syndrome [5]. Both Rotor syndrome and Dubin-Johnson syndrome do not have any specific therapy since they are benign conditions.

When considering the differential diagnosis of hyperbilirubinemia syndrome over all, they should be characterized as either unconjugated or conjugated hyperbilirubinemia. The causes of conjugated hyperbilirubinemia are mentioned above, where as the differential diagnoses for unconjugated hyperbilirubinemia include, but are not limited to, Gilbert's syndrome, hemolysis, Crigler-Najjar syndrome, hyperthyroidism and states that impair hepatic bilirubin uptake (i.e. drugs or reduced hepatic perfusion).

Our patient was thought to have septic shock from cholangitis and hyperbilirubinemia. It turned out he was actually having recurrent pneumonias leading to hemodynamic instability in the setting of his congenital benign hyperbilirubinemia. As seen in our case, this diagnosis is often misdiagnosed as a more severe form of hepatobiliary disease. A heightened awareness of these diagnoses is essential when treating individuals with hyperbilirubinemia in order to prevent unnecessary interventions and potential complications.

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