

Single Case

Rotor Syndrome Presenting as Dubin-Johnson Syndrome

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Keywords

Conjugated hyperbilirubinemia · Dubin-Johnson syndrome · *ABCC2*/*MRP2* · Rotor syndrome · *SLCO1B3*/*OATP1B*

Abstract

A 42-year-old man with no relevant past medical history presented with intermittent mild icterus and no signs of chronic liver disease. Laboratory tests were notable for hyperbilirubinemia (total 7.97 mg/dL, direct 5.37 mg/dL), bilirubinuria, no signs of hemolysis, normal liver tests and lipids profile. Abdominal ultrasound was unremarkable. A panel of chronic liver diseases was negative except for increased serum (147.4 µg/dL) and urinary (179 µg/24 h) copper, with normal ceruloplasmin. No other Leipzig criteria for Wilson's disease were found, including a negative test for *ATP7B* gene mutations (by exome sequencing). Total urinary coproporphyrin was normal with predominance of isomer I (86% of total urinary coproporphyrin output). Clinical and laboratorial profile was compatible with Dubin-Johnson syndrome; however, exome sequencing and search for deletions in the *ABCC2* gene (encoding *MRP2*) only found a heterozygous potentially pathogenic variant (c.1483A>G – p.Lys495Glu). Additional extended molecular analysis of genes implicated in bilirubin metabolism found a homozygous deletion of a region encompassing exons 4–16 of *SLCO1B3* gene (encoding *OATP1B3*) and all *SLCO1B1* exons (encoding *OATP1B1*), thereby establishing Rotor syndrome diagnosis. Rotor and Dubin-Johnson syndromes are rare autosomal recessive liver diseases characterized by chronic conjugated hyperbilirubinemia, caused by the absence of the hepatic function *OATP1B1/B3* (leading to impaired hepatic bilirubin reuptake and storage) and *MRP2* transporters (leading

to impaired hepatic bilirubin excretion), respectively. We report a case of compound hereditary hyperbilirubinemia with a misleading presentation with special focus on its diagnosis, particularly the advantage of extensive unbiased genetic testing by dedicated laboratories. With this case, we aim to highlight the necessity of establishing a diagnosis, reassuring the patient, and avoiding unnecessary invasive and costly diagnostic procedures.

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Introduction

Elevation of plasma/serum bilirubin concentration is often encountered in everyday clinical practice. Understanding the relative likelihood of different disease processes can help to investigate and establish the diagnosis appropriately. Inherited disorders of bilirubin metabolism result in either a reduced bilirubin uptake by hepatocytes, bilirubin conjugation, hepatocyte storage, or secretion of bilirubin into bile. Two known inherited disorders manifest by isolated conjugated hyperbilirubinemia: Dubin-Johnson syndrome (DJS) and Rotor syndrome (RS). Although uncommon, their diagnosis is crucial since differentiation from other more serious disorders can prevent these patients from unnecessary procedures and anxiety.

DJS is a rare underdiagnosed disorder, which consists of hereditary hyperbilirubinemia, characterized by mild elevation of conjugated bilirubin and no other signs of hepatic injury, due to a defect on the multidrug resistance-associated protein 2 (MRP2). Liver biopsy in DJS is characteristic for the accumulation of a dark, granular pigment in centrilobular hepatocytes in an otherwise normal liver. RS is a familial condition with autosomal recessive transmission, where hepatic reuptake and storage are impaired due to a defect in the organic anion transporting polypeptide 1B1 and 1B3 transporters (OATP1B1 and OATP1B3, respectively) [1]. Biologically, urinary coproporphyrin excretion distinguishes them: in RS, total coproporphyrin urinary excretion is increased 2- to 5-fold being 65% coproporphyrin I, and in DJS, urinary coproporphyrin levels are normal, but being over 80% coproporphyrin I [2]. We aimed to describe a case of complex hereditary hyperbilirubinemia with a misleading presentation, highlighting the necessity of in-depth genetic testing.

Case Report

An otherwise healthy 42-year-old Caucasian man presented mild intermittent icterus and fatigue. He denied abdominal pain, fever, pruritus, choloria, acholia, or other symptoms. Consumption of alcohol, tobacco, prescribed or over-the-counter medicines was also excluded. Apart from scleral icterus, physical examination was unremarkable, with no stigmata of chronic liver disease. Laboratory tests were notable for hyperbilirubinemia (total 7.97 mg/dL and direct 5.37 mg/dL) and bilirubinuria, no signs of hemolysis, normal liver tests (AST 21 U/L, ALT 32 U/L, GGT 21 U/L, ALP 74 U/L, albumin 5.3 g/dL, PT 12.5 s) and lipids profile. Abdominal ultrasound was unremarkable. A panel of chronic liver diseases (viral, autoimmune, and metabolic) was negative except for increased serum (147.4 µg/dL) and urinary (179.9 µg/24 h) copper, with normal ceruloplasmin levels. No other Leipzig criteria for Wilson's disease were found, including a negative genetic test for *ATP7B* gene variants (by exome sequencing). Coproporphyrin analysis showed that total urinary coproporphyrin level was normal with predominance of isomer I (86% of total). The clinical and laboratorial profile

was compatible with DJS; however, only a heterozygous variant of the *ABCC2* gene encoding MRP2 (c.1483A>G – p.Lys495Glu) was found. Additional molecular studies revealed a homozygous deletion of a genomic region encompassing exons 4–16 of *SLCO1B3* gene (encoding OATP1B3) and all exons of *SLCO1B1* (encoding OATP1B1), consistent with RS diagnosis.

Discussion

We present a patient with predominantly conjugated hyperbilirubinemia but otherwise normal liver tests, increased urinary copper and urinary coproporphyrin isomer I fraction. Normal serum haptoglobin and blood film excluded hemolysis; clinical and imaging investigations did not show any signs of biliary obstruction. However, specific biliary imaging such as MRCP was not performed which might be pointed out as a limitation of this report as well as the lack of a histological analysis to promptly exclude DJS. Considering the presented data, rare inherited disorders of bilirubin metabolism were hypothesized, DJS being the most likely diagnosis since an inverted ratio of urinary excreted coproporphyrin isomers I and III was found. Under normal circumstances, coproporphyrin I is preferentially excreted in bile (accounting for 65% of biliary coproporphyrin), whereas coproporphyrin III isomer is preferentially eliminated in urine (accounting for 75% of urinary coproporphyrin). Several hepatobiliary disorders, including cholestasis, present increased total urinary coproporphyrin, reflecting the diversion into urine of material normally excreted into bile, with an increase in the urinary proportion of isomer I, which is almost always below 65% of total. In DJS, total urinary coproporphyrin excretion is normal but over 80% is excreted as coproporphyrin I, due to an increased reflux of isomer I back into the sinusoid [3]. The initial genetic approach consisted of exome sequencing and deletion search on *ABCC2* gene, finding only a heterozygous variant, which could not confirm the clinical suspicion of DJS, an autosomal recessive condition. Afterward, a multigene panel evaluation unexpectedly found a newly reported deletion encompassing *SLCO1B1* whole-gene and exons 4–16 of *SLCO1B3*, which results in complete OATP1B1 and OATP1B3 deficiency, and confirmed the diagnosis of RS. Urinary excretion of coproporphyrins is the most important diagnostic tool to differentiate DJS from RS. Contrary to DJS, in RS, total coproporphyrin excretion in urine is increased and isomer I is usually <75–80%, in line with the interaction of several porphyrins with OATP1B1 [4]. The phenotypical pattern showed in this RS case might be due to modulation of porphyrin excretion by the heterozygous variant of *ABCC2* (c.1483A>G). Additionally, the degree of cupruria observed in this case makes it a unique presentation of RS. Wilson's disease was extensively excluded, not fulfilling Leipzig criteria and after negative genetic testing for *ATP7B* gene mutations. One explanation for cupruria in this patient could be the heterozygous mutation of *ABCC* gene, which might preclude the alternative biliary excretion pathway of copper [5] coupled with the reuptake defect from RS resulting in copper accumulation in circulating plasma and subsequent increased urinary excretion. Although benign and rare, establishing RS or DJS diagnosis is crucial to reassure the patient, avoid unnecessary invasive and costly diagnostic procedures, and to prevent decompensation during intercurrent illness, pregnancy, or drug toxicity risks.

Statement of Ethics

Ethical approval is not required for this study in accordance with local and/or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mariana Morais wrote the manuscript. Philippe Couvert performed genetic analysis and revised the manuscript. Isabelle Jéru and Mariana Verdelho Machado revised the manuscript.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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