https://doi.org/10.22516/25007440.1275

Case report

Diagnosis of Dubin–Johnson Syndrome in an Adult Patient: A Case Report

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Citation:
Torres-Gil AD, Muñoz-Torres J. Diagnosis of Dubin–Johnson Syndrome in an Adult Patient: A Case Report. Revista. colomb. Gastroenterol. 2025;40(3):357-361. https://doi.org/10.22516/25007440.1275

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Received: 16/08/2024
Accepted: 21/02/2025

Abstract

Dubin–Johnson syndrome (DJS) is an inherited disorder caused by a genetic mutation in the *ABCC2* gene, which affects the synthesis of the MRP2 transport protein. This results in impaired excretion of direct bilirubin from hepatocytes. As DJS is a rare condition, it is usually diagnosed incidentally, which may initially lead to confusion with other clinical entities. We present the case of a 40-year-old man with an atypical and nonspecific clinical presentation, characterized by isolated elevation of direct bilirubin without impairment of liver function. Liver biopsy revealed findings consistent with DJS. Although DJS does not require specific treatment, early diagnosis is crucial to avoid unnecessary invasive procedures and to rule out conditions requiring targeted therapies, thereby preventing progressive liver damage.

Keywords

Jaundice, biopsy, hyperbilirubinemia, Dubin–Johnson syndrome.

INTRODUCTION

Dubin-Johnson syndrome is a rare, hereditary disorder[(1)] characterized by chronic, intermittent non-hemolytic hyperbilirubinemia[(2-5)]. It was first described in 1954 in adults[(1)] and occurs in approximately two cases per 100,000 inhabitants[(2-5)]. The pathophysiology of this entity is related to a mutation in the *ABCC2* gene[(2,3,6,7)], which encodes the MRP2 transporter protein. This protein plays a crucial role in secreting direct bilirubin out of hepatocytes into the bile canaliculi[(2)]. Consequently, this genetic mutation causes a blockage in bilirubin excretion, triggering intracellular accumulation and subsequent diffusion into the circulation, where it is detected in the serum; laboratory tests reveal this characteristic pattern of mildly elevated direct bilirubin in the absence of other abnormalities in liver biochemical tests[(2-5)]. Dubin-Johnson syndrome is generally asymptomatic, but it can present with symptoms such as asthenia, anorexia, abdominal pain, hepatomegaly, dark urine, nausea, vomiting, or diarrhea[(2,6)].

The diagnosis of the syndrome is most often made as an incidental finding during adolescence or in young adults[(2)]. It is also diagnosed through laboratory tests, histological studies, and macroscopic liver findings. Liver biopsy shows the accumulation of dark pigment and brown melanin-like granules in the lysosomes of centrilobular hepatocytes[(2,4-6,8)]. The liver exhibits a characteristic blackish discoloration in this pathology[(3)]. Furthermore, urine tests have been used to assess the excretion of urinary coproporphyrins, which show a significant increase (>80%) in the type I isomer compared to normal values (45%) and a reduction in the elimination of the type III isomer[(3,4,6)]. Meanwhile, the

bromsulphalein clearance test, previously considered the gold standard for diagnosis, has been withdrawn from the market due to associated adverse effects, including the risk of respiratory and cardiac failure and anaphylactic shock[4].

CASE PRESENTATION

A 40-year-old male patient with a history of Gilbert's syndrome (diagnosed in childhood) and cholecystectomy at age 9 for cholelithiasis presented to the emergency department with multiple episodes of vomiting associated with diarrhea and right upper quadrant abdominal pain. Physical examination revealed pain on palpation in the upper abdomen, a negative Murphy's sign, and a slight icteric tint in the sclera and skin.

From a paraclinical perspective, serial reports during hospitalization showed persistent mixed hyperbilirubinemia with a predominance of direct bilirubin. The rest of the liver biochemical tests were within normal limits, except for a mild elevation of alanine aminotransferase (ALT) upon admission to the institution, which was attributed to the presence of hepatic steatosis (assessed by ultrasound) and subsequently normalized (**Table 1**). Furthermore, secondary infection by hepatotropic viruses and autoimmune hepatitis were ruled out (**Table 2**). The observed cholestatic pattern suggested the possibility of a biliary obstructive syndrome, so a magnetic resonance cholangiopancreatography was performed. This test demonstrated that the intra- and extrahepatic bile ducts had a normal caliber, with a common bile duct diameter of 3 mm, and a moderate increase in the size of the liver and spleen was observed.

Given the persistence of chronic hyperbilirubinemia (for one year) predominantly due to direct bilirubin, without other abnormalities in the liver panel and absence of evidence of autoimmune, infectious, or structural involvement on imaging, the accuracy of the initial diagnosis of Gilbert's syndrome was questioned. Considering the possibility of a different hereditary metabolic pathology, a percutaneous liver biopsy was suggested to obtain a more precise diagnosis and guide appropriate management.

Following the receipt of the histopathological report of the liver biopsy (**Figure 1**), the diagnosis of Dubin-Johnson syndrome was confirmed, which was found to be consistent with the clinical symptoms and previously described paraclinical findings.

Portal triads of usual morphology with present ducts and vessels without lobular alterations showed preserved architecture with usual trabecular architecture; some triads showed a very discrete, scattered mononuclear inflammatory infiltrate, and the presence of only an ochre-colored

Table 1. Laboratory Record

Test	Previous Hx (09/03/2020)	First Control (06/12/21)	Second Control (08/12/21)	Third Control (10/12/21)
Complete Blood Count	WBC: 12,100, N: 91.1%, Hb: 17, Hct: 50.2%, PLT: 314,000	WBC: 6900, N: 62%, Hb: 16.2, Hct: 46%, PLT: 262,000		WBC: 5700, N: 62%, Hb: 15.1, Hct: 44.3%, PLT: 328,000
CRP		61.3		
Amylase	93	50		
ALT		52	33	37
AST		39	25	33
Total Bilirubin	8.43	10.8	9.6	8.32
Indirect Bilirubin	2.72	3.26		2.1
Direct Bilirubin	2.41	7.6	7.5	6.0
Alkaline Phosphatase		77	58	62
GGT			66	
PT				10.9
Albumin				4
Creatinine	0.7	0.70		
BUN	19	11		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GGT: γ-glutamyl transferase; Hb: hemoglobin; Hct: hematocrit; N: neutrophils; PLT: platelets; CRP: C-reactive protein; PT: prothrombin time; WBC: white blood cells. Table prepared by the authors.

Table 2. Infectious and Immunological Profile

Test	Result
Anti-smooth muscle antibody	Negative: titer less than 1/20
Antinuclear antibody	Negative
Hepatitis C antibody	0.01
Hepatitis A IgG	0.35 (non-reactive)
Anti-HBc IgM	0.03 (non-reactive)

Hb: hemoglobin; IgG: immunoglobulin G; IgM: immunoglobulin M.

intracytoplasmic pigment, reminiscent of lipofuscin in small granules and which was negative with iron staining, was notable. The Masson-Fontana stain was positive for the described ochre pigment. There was no degree of fibrosis.

DISCUSSION

Dubin-Johnson syndrome is a rare, hereditary entity, with an estimated prevalence of less than 1 case per 100,000 inhabitants in the general population. However, a higher prevalence has been reported in Jewish and Iranian populations in the Middle East and Asia, with a frequency of approximately 1 case per 1,300 inhabitants[3]. Due to its low frequency and lack of awareness, Dubin-Johnson syndrome is an underdiagnosed condition that requires, on average, 13 years from the onset of symptoms to reach an accurate diagnosis. Dubin-Johnson syndrome typically manifests in adolescence or young adulthood, usually in the second decade of life, with an earlier onset in males[2].

Regarding the clinical picture, most patients with Dubin-Johnson syndrome are asymptomatic, and the diagnosis is made incidentally on routine laboratory tests, which show a predominant elevation of the direct bilirubin fraction (>50% of the total) and bilirubin levels typically ranging from 2 to 5 mg/dL[2]. However, in some cases, Dubin-Johnson syndrome can present with symptoms, including mild jaundice, weakness, abdominal pain, diarrhea, and localized pain in the right upper quadrant[3].

The first description of this pathology dates back to 1954, when a histological study of liver biopsies revealed the presence of a strange intracellular pigment in 12 patients with mild, chronic, non-hemolytic direct hyperbilirubinemia

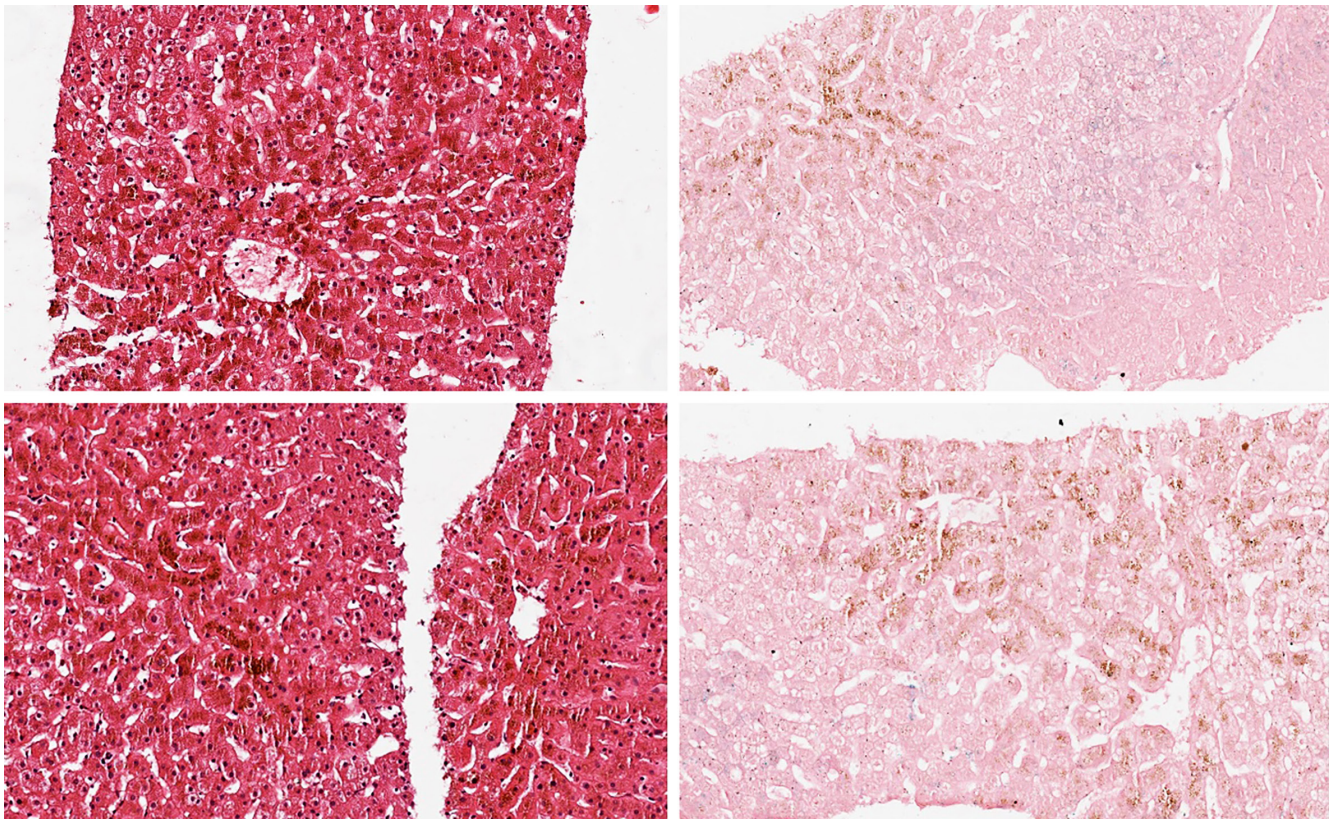

Figure 1. Liver biopsy of the patient with Dubin-Johnson syndrome. Images property of the authors.

without an apparent cause[1,2,7]. Subsequently, other studies confirmed the presence of dark deposits of melanin-like lysosomal pigment, suggesting the existence of a new, previously undescribed clinico-pathological entity.

It is now known that Dubin-Johnson syndrome is an autosomal recessive liver disease caused by a defect in the *ABCC2* gene[6,7]. Various mutations in this gene have been identified, including deletions, nonsense mutations, and splice-site mutations[6], resulting in impaired synthesis of the MRP2 protein. This protein plays a crucial role in transporting substances essential for the secretion of direct bilirubin out of the hepatocyte into the biliary collecting system[2].

The most recent research has focused on the genetic component of the disease, finding that a large proportion of cases present with typical clinical features, two mutated *ABCC2* alleles, and high genetic homogeneity. The aim is to deepen the understanding of the relationship between different mutation variables and the different genotypes and presentation phenotypes, especially in patients with neonatal cholestasis.

Togawa et al.[7] conducted a multicenter study on neonatal Dubin-Johnson syndrome and demonstrated that only 38% of the individuals analyzed with a positive genetic diagnosis presented typical histological findings and macroscopic characteristics. This suggests there is a variant of clinical presentation in neonates with cholestasis that is not the typical form of the syndrome. Furthermore, it was found that melanin-like pigment deposits in hepatocytes accumulate gradually after birth, which gives value to genetic and immunohistochemical tests, especially in the context of atypical presentations such as in neonates[7].

This case is noteworthy due to the presentation of clinical manifestations that are uncommon for Dubin-Johnson syndrome, particularly the late onset of these manifestations compared to what is reported in the literature[2,3]. Additionally, the case presents the cardinal paraclinical pattern characteristic of this disease, which is isolated direct hyperbilirubinemia. This alteration is typical of hereditary pathologies of bilirubin metabolism and excretion, such as Dubin-Johnson syndrome and Rotor syndrome[9]. The histopathological finding of a positive Masson-Fontana stain for the ochre pigment in centrilobular cells is characteristic of Dubin-Johnson syndrome[10], as this intracytoplasmic pigment is not found in Rotor syndrome[1,2]. These findings are sufficient to confirm the diagnosis of Dubin-Johnson syndrome.

Dubin-Johnson syndrome is an uncommon clinical entity that, due to its asymptomatic nature or non-specific presentation, is often underdiagnosed or confused with other diagnoses. This can lead to unnecessary invasive procedures, which carry risks and financial costs. Although it is a benign disease that does not progress to fibrosis or cirrhosis and does not require specific treatment[2], an accurate diagnosis is crucial to rule out other causes of clinical jaundice that can have a significant impact on morbidity and mortality[4]. A timely diagnosis allows for the provision of appropriate treatment and improves the prognosis of similar pathologies.

CONCLUSIONS

Dubin-Johnson syndrome is a rare hereditary pathological entity that, due to its asymptomatic nature or non-specific presentation, is often misdiagnosed and found as an incidental finding. Therefore, it is essential to suspect this condition to rule out other hepatobiliary disorders that could cause liver injury, to identify those patients who may be potentially treatable, and to avoid performing unnecessary invasive procedures. Liver biopsy is a safe and definitive diagnostic method for identifying this pathology.

Conflicts of Interest

The authors declare no conflicts of interest.

Sources of Funding

None.

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