Case Report: Dubin-Johnson Syndrome Presenting With Infantile Cholestasis: An Overlooked Diagnosis in an Extended Family

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Dubin-Johnson syndrome (DJS) is an often-missed diagnosis of neonatal cholestasis. We report two patients with DJS, who presented with neonatal cholestasis. The first patient underwent extensive investigations for infantile cholestasis with no definitive etiology reached; the diagnosis of DJS was missed until the age of 14 years old. The diagnosis was confirmed genetically with c.2273G > T, p.G758V mutation in exon 18 of the ABCC2 gene. The 2nd patient is a 7-day-old baby, the son of the 1st patient who gave birth to him at the age of 21 years old. He was diagnosed with DJS at the age of 2 weeks based on normal clinical and laboratory workup apart from direct hyperbilirubinemia. He had the same mutation as his mother in homozygous status. The husband was heterozygous for the same mutation. DJS is one of the often-missed differential diagnoses of neonatal cholestasis. It should be suspected in patients of infantile cholestasis, who have an, otherwise, normal physical examination, and laboratory investigations to avoid unnecessary lengthy, invasive, and expensive workups.

Keywords: Dubin-Johnson syndrome, infant, cholestasis, ABCC2 gene, mutation

INTRODUCTION

Dubin-Johnson syndrome (DJS) was first reported in 1954 by Dubin and Johnson (1) as a rare autosomal recessive disease with clinical features of chronic-conjugated hyperbilirubinemia due to a defect in the excretion of the anionic conjugate from the hepatocytes into the bile (2). Most patients manifest as intermittent or chronic jaundice aggravated by intercurrent illness (1). Physical examination is frequently unremarkable (1). Liver enzymes are usually within normal limits, while bilirubin levels fluctuate (1).

The syndrome occurs due to expression defects of the MRP2 gene, an ATP-dependent canalicular membrane transporter (3–5). The diagnosis is established by performing the bromsulphalein test, oral cholecystography, HIDA scan, and liver biopsy (6–8). Liver biopsy is the
gold standard diagnostic test for this syndrome. It shows
the presence of brown pigment granules in the centrilobular
hepatocytes (9–11). Molecular genetic testing of the ABCC2 gene
is the definitive diagnosis (12). We, herein, report a Saudi female
child who presented as having cholestasis at the age of 1 month
with a missed diagnosis of DJS until the age of 14 years. Her
molecular genetic testing revealed the c.2273G > T, p.G758V
mutation in Exon 18 of the ABCC2 gene.

CASE REPORT

A 14-year-old female child was born to consanguineous Saudi
first-degree cousins who are descents from a tribe with highly
consanguineous marriage. She was referred to a pediatric
gastroenterology clinic as a case of persistent conjugated
hyperbilirubinemia for investigations.

Tracing her history revealed that jaundice started at the
age of 4 days with elevated total bilirubin (350 µmol/L),
mainly indirect. Her direct bilirubin was 30 µmol/L with
normal alanine and aspartate transaminases (ALT and AST). Phototherapy was started, and the patient was discharged in good
condition after 3 days.

She returned to her primary physician at the age of 40 days
with unresolved jaundice and mild abdominal distension with
no organ enlargement. Her investigations revealed mild direct
hyperbilirubinemia. Her total and direct bilirubins were 50
and 35 µmol/L, respectively. Her ALT, AST, gamma-glutamyl
transpeptidase (GGT), prothrombin time/concentration, and
abdominal ultrasonography were all normal. Extensive workups
of cholestasis, including complete blood count, retics, coombs,
hemoglobin electrophoresis, urine and blood cultures, TORCH
screening, serum bile acids, thyroid profile, tandem metabolic
screening, and non-glucose-reducing substances in the urine,
were all normal. HIDA scan and MRCP were not available
in that hospital and were not done. Liver biopsy was refused
by the parents, and she was discharged against medical advice
in good general condition without a definitive diagnosis. Her
total and direct bilirubin at time of discharge was 48 and 40
µmol/L, respectively.

Since that time and until her presentation to our care at the age
of 14 years, the parents used to visit different health care facilities
when their child’s jaundice deepened with different intercurrent illnesses. Laboratory workups, including liver function tests and
hepatitis markers, were done many times with normal results
apart from direct hyperbilirubinemia.

On presentation to our hospital, she had tinge jaundice
with stable vital signs, normal abdominal examination with no
organomegaly, and normal assessment of different body systems.
Her laboratory investigation showed high total bilirubin of 32
µmol/L, mainly in the form of direct bilirubin (31 µmol/L), with
normal ALT, AST, GGT, complete blood picture, and a renal
profile with normal abdominal US. The diagnosis of DJS
was suspected, and a 99mTc-HIDA scan was requested. The HIDA
scan serial images revealed rapid clearance of blood pool activity
with a good hepatocyte function as evidenced by the adequate
ascending limb of the dynamic curve. However, there was a slow
excretion of radioactivity into the biliary radicles with retained
activity in the liver up to 6 h. The gall bladder was seen at 1 h and
the small intestine at 2 h. This good hepatocyte uptake function
with impairment of excretory function in absence of obstruction
was highly suggesting DJS. Urinary coproporphyrins were not
done (the test was not available in our hospital).

Molecular genetic testing for DJS, the ABCC2 gene, was
requested to confirm the diagnosis.

MOLECULAR GENETIC ANALYSIS OF
THE ABCC2 GENE

PCR amplification and direct sequencing of all coding exons
and flanking intronic sequence (ABCC2 gene, GenBank
NM_000392.3, NC_000010.10) gene dosage analysis by
quantitative real-time PCR (qPCR) with 5 amplifications
(in exons 1, 7, 15, 24, and 32) (13).

RESULTS

Unclassified variant c.2273G>T, pG785V in Exon 18 of the gene
ABCC2 gene in the homozygous state. By qPCR, no deletion or
duplication was detected, Figure 1.

INTERPRETATION

Molecular analysis confirmed the clinical suspicion of DJS
syndrome. The variant c.2273G>T, pG785V in Exon 18 of the gene
ABCC2 gene was detected in homozygous state.

The patient was diagnosed in 2014, and, at that time, this
mutation was a novel mutation, which has not been described
yet (HGMD professional 2014.2). “Polyphen2” (14) predicts the
consequence of pG785V for the ABCC2 protein as “probably
damaging” and “mutation taster” (15) called the variant “disease-
causing” At that time, we assumed that the variant represented
a pathogenic mutation, but the parents’ missed follow-up with
their child, and we failed to outreach to them to get consent for
publication. Hence, we could not publish our case report at the
time of detection of the novel mutation.

In October 2021, the parents presented to us once again
with the patient who was a 21-year young adult female. She
had married to her cousin, and she experienced an intermittent
deepening of her jaundice during pregnancy with no associated
pruritus or dark urine. Her liver biochemistry was within normal
values apart from direct hyperbilirubinemia.

She gave birth to a 3.5 kg male baby by normal vertex
delivery with uneventful antenatal and perinatal histories. Her
baby developed jaundice at the age of 1 week with no history of
pallor, blood transfusion, or medications intake.

At the age of 4 weeks, she thought about our medical
advice for her newly born jaundiced baby. On assessment, his
physical examination was normal apart from mild jaundice
with no organomegaly. His workup was assuring with normal
abdominal ultrasound, ALT, AST, albumin, prothrombin
time/concentration, and GGT with a high total bilirubin of 78 µmol/L and high direct bilirubin of 43 µmol/L, suggesting the diagnosis of DJS.

Sanger sequencing of the p.G785V variant detected in his mother was performed for him, which came out to be positive. The husband was also tested and was heterozygous for the same mutation.

In January 2022, we got the consent of the patient and her husband for publishing their family case series. The family pedigree is illustrated in Figure 2.
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