Dubin-Johnson syndrome in Tunisia: Spectrum of a rare disease

Syndrome de Dubin-Johnson en Tunisie : spectre d’une maladie rare

Introduction

Dubin-Johnson syndrome (DJS) is a benign autosomal recessive disorder caused by mutations in the ATP-binding cassette subfamily C member 2 (ABCC2)/multidrug resistance-associated protein 2 (MRP2) gene, which cause either absent or deficient expression of this transporter protein [1,2]. This protein acts as a pump to transport substances out of the liver, kidneys, intestine, or placenta, and which absence results in impaired transport of bilirubin into bile and excretion of bile acids after sulfation or glucuronidation. As a result, bilirubin accumulates in the body, causing a chronic, predominantly conjugated hyperbilirubinemia, alteration in coproporphyrin metabolism, and intracellular deposition of a dark melanin-like pigment giving the liver a typical black cast [3]. Patients with DJS exhibit mild to moderate recurrent jaundice. Jaundice is typically the only symptom of DJS, but some people also experience fatigue, mild upper abdominal pain, nausea, and/or vomiting. This case report describes DJS in a 9-year-old boy with jaundice since childhood.

This child was born to related parents with no family history for liver disease. He was born after a full-term and uneventful pregnancy. He had no history of any drug use or hepatobiliary diseases. He had amid jaundice since the age of 2 years. He had no complaint of pruritus, abdominal pain or gastrointestinal bleeding. Clinical examination showed an eutrophic child with no dysmorphic features. He was jaundiced. The abdominal examination showed a mild-nontender and smooth hepatomegaly. The spleen was not palpable. Examination of other systems showed nothing abnormal. His liver function tests showed a total serum bilirubin level of 12.41 mg/dL (normal, 0 to 12.1 mg/dL) and conjugated bilirubin level 10.1 mg/dL (normal, 0 to 2.31). The liver enzymes, total proteins and albumin were normal. Peripheral blood film showed no haematological signs attributed to hemolysis and differential WBC counts and platelet count were normal. Serologic screening tests for hepatotropic viruses (hepatitis A, B, and C; Epstein-Barr virus; and cytomegalovirus) were negative. Anti-smooth muscle antibodies, anti-mitochondrial antibodies, anti-liver kidney microsome type 1, and anti-nuclear factor were all negative. In the recent past 3 years total hyperbilirubinemia occurs intermittently, with a predominance of the direct fraction. Abdominal sonography revealed nothing significant but mild hepatomegaly with heterogeneous echopattern. Urinary coproporphyrin levels revealed an increase of isomers I representing 90%, compatible with a diagnosis of DJS. Liver biopsy was not done. After informed consent, peripheral blood samples were collected from the proband and his parents. DNA extraction was performed following the standard phenol-chloroform method for molecular genetic studies of the ABC2 gene. Sanger sequencing of the coding regions, splice sites and parts of introns of ABCC2 indicated the presence of a novel homozygous non sense mutation c.3599G>A(p.W1200X) in exon 25. Besides, we showed the presence of a known polymorphism rs927344 c.116 T>A (p.Y39F) in exon 2 and an unknown homozygous substitution c.3424G>C (p.V1142L) in exon 25. Bioinformatic tools such as polyphen 2 (http://genetics.bwh.harvard.edu/phh2/) and SIFT (http://sift.bii.a-star.edu.sg/) predicted that this substitution is tolerated. We also sequenced exons 2 and 25 in both parental DNA samples. Both parents turned to be heterozygotes for each of the three variations. We thus conclude that the non-sens mutation is responsible of the phenotype of our patient. Taken together, our data confirm the clinical and laboratory diagnosis of Dubin-Johnson type hereditary jaundice in the index patient. His parents are asymptomatic heterozygotes for a causative mutation for this disorder.

Discussion

DJS is a rare autosomal recessive disorder caused by mutations in the ABCC2/multidrug resistance-associated protein 2 (MRP2) gene, which is located at 10q24. Several different mutations have been described in DJS patients, including exon skipping, nonsense, and/or base deletion. Most mutations result in stop codons and failure of MRP2 transcription. Less frequently, they can result in endoplasmic reticulum retention of MRP2 and failure of translocation to the canalicular membrane [2]. To our knowledge only nine cases have been reported in Tunisia [4,5]. Despite the genetic nature, there are reported cases with no family history of the disease. In the present study, the patient was born to consanguineous parents and did not report any family history of symptoms consistent with the syndrome. Genetic analysis showed a homozygous non-sens mutation which is responsible of a production of truncated protein and thus causes DJS in our patient. This mutation was inherited from his parents. Our findings underline the impact of consanguinity on the occurrence of rare AR diseases in populations with high consanguinity rates.
In this syndrome, jaundice begins in infancy, at around two years of age. Clinical features of DJS includes intermittent continuing or recurrent episodes of mild jaundice. Occasionally patients complain of weakness and vague abdominal pain, and hepatosplenomegaly is rarely observed. Therefore, there is no need for hospitalization and regarding to the single DJS, treatment is usually unnecessary because the favorable prognosis. Actually, most DJS patients have a normal life span. Bilirubin levels are usually in the range of 2–5 mg/dL, mostly conjugated bilirubin and the results of liver enzymes are mostly normal. Abnormal distribution of the coproporphyrin isomers I and III in the urine is a characteristic feature of DJS. The urinary excretion rate of coproporphyrin isomer I is > 80% of the total urinary coproporphyrin while total urinary excretion of coproporphyrin is normal or slightly elevated [6]. Urinary coproporphyrin isomer I excretion is approximately 40% in carriers. The noninvasive DNA analysis is the method of choice whenever the diagnosis is unclear in subjects with suspected hereditary hyperbilirubinemia, no matter the type. The indications for liver biopsy should then be considered only if the results of genetic investigation are inconclusive [7]. Liver histology in DJS shows an accumulation of distinctive melanin-like lysosomal pigment in an otherwise normal liver, which gives the organ a characteristic slate gray or even black color [8,9].

**Conclusions**

Dubin-Johnson syndrome is a rare benign condition that requires no specific therapy. Once this diagnosis is made, patient must be reassured of its benign nature, excellent prognosis and normal life expectancy.

**Disclosure of interest:** The authors declare that they have no competing interest.

**References**


