A Tunisian case of a rare cause of mixed hyperbilrubinemia : A Rotor Syndrome

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ABSTRACT

Rotor syndrome is a benign autosomal recessive disease and a rare cause of mixed direct and indirect hyperbilirubinemia. We reported a case of a 20-day-old girl withjaundicesincebirth.Shewaseutrophicchildwithdymorphicfeatures. She had no hepatomegaly and no splenomegaly. Liver function tests showed only elevation of predominantly conjugated bilirubin. Other laboratory findings were normal. She had several explorations and they were all normal. DNA extraction indicated that the child was homozygous for a deletion of a fragment of chromosome 12 of more than 400 kb encompassing the entire SLCO1B1 gene, the entire SLCO1B7 gene and exon 4 to 16 of the SLCO1B3 gene. Our data confirm the clinical and laboratory diagnosis of Rotor Syndrom. Rotor syndrome is largely a diagnosis of exclusion. This is a benign disease, which does not require therapeutic management, hence the benefit of an early diagnosis which will prevent unnecessary explorations.

RÉSUMÉ

Le syndrome de Rotor est une maladie hépatique héréditaire bénigne et très rare. Elle se manifeste par une hyperbilirubinémie chronique à prédominance conjuguée. Nous rapportons le cas d'une fille de 20 jours, qui s'est présentée avec un ictère et une dysmorphie faciale. Elle n'avait pas d'hépatomégalie, ni de splénomégalie. Le bilan hépatique avait montré une hyperbilirubinémie à prédominance conjuguée. Le bilan biologique était par ailleurs sans anomalies. Elle a bénéficié de plusieurs examens complémentaires, qui étaient tous normaux. Au terme de ce bilan négatif, une extraction d'ADN a été effectuée objectivant une homozygotie pour une délétion d'un fragment du chromosome 12 de plus de 400 kb englobant la totalité du gène SLCO1B1, la totalité du gène SLCO1B7 et les exons 4 à 16 du gène SLCO1B3. Ce génotype est compatible avec un syndrome de Rotor. Ce diagnostic reste un diagnostic d'élimination. Il s'agit d'une maladie bénigne, qui ne nécessite pas de prise en charge thérapeutique, d'où l'intérêt d'un diagnostic précoce qui permettra d'éviter des explorations inutiles.

INTRODUCTION

Rotor syndrome is a benign autosomal recessive disease and a rare cause of mixed direct and indirect hyperbilirubinemia. To date, less than 100 cases have been reported in the literature. The disease is characterized by non-hemolytic jaundice due to chronic elevation of predominantly conjugated bilirubin [1]. This phenomenon is a result of impaired hepatocellular storage of conjugated bilirubin that leaks into plasma causing hyperbilirubinemia. 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.

CASE REPORT

We herein present a case of a 50-day-old girl with jaundice since birth. She was born to related parents with no family history for hepatobiliary disease. She was born after a full-term and uneventful pregnancy. She had a mild jaundice since birth. Clinical examination showed an eutrophic child without dysmorphic features: wide forehead, horizantal eyelid clefts, anteverted nostrils, small mouth, microretrognatism and normal ears. She was jaundiced. The abdominal examination showed no hepatomegaly. The spleen was not palpable. Examination of other systems showed nothing abnormal. His liver function tests showed a total serum bilirubin level of 168 µmol/l and conjugated bilirubin level 143 µmol/l. The liver enzymes, total proteins and albumin were normal. Peripheral blood film showed no hematological signs attributed to hemolysis and differential white blood cells counts and platelet count were normal. Concerning liver function tests and etiological assessment : a cytobacteriological examination of the urine was normal as well as a thyroid workup. Abdominal sonography was normal. We completed with a spinal x-ray that didnt show butterfly wing vertebrae. Electrocardiography revealed nothing significant except a patent foramen ovale. The ophtalmologic examination was normal. Liver biopsy was not done. DNA extraction indicated that the child was homozygous for a deletion of a fragment of chromosome 12 of more than 400 kb encompassing the en-

tire SLCO1B1 gene, the entire SLCO1B7 gene and exon 4 to 16 of the SLCO1B3 gene. We also sequenced the both parental DNA samples. They turned to be heterozygote for the variation. We thus conclude that the mutation is responsible of the phenotype of our patient. Taken together, our data confirm the clinical and laboraty diagnosis of Rotor Syndrom type hereditary jaundice in the index patient. His parents are asymptomatic heterozygotes for a causative mutation for this disorder.

DISCUSSION

Rotor syndrome is a rare, inherited, autosomal recessive disorder. The SLCO1B1 and SLCO1B3 genes are involved in Rotor syndrome. Mutations in both genes are required for the condition to occur. The SLCO1B1 and SLCO1B3 genes provide instructions for making similar proteins, called organic anion transporting polypeptide 1B1 (OATP1B1) and organic anion transporting polypeptide 1B3 (OATP1B3), respectively. They transport bilirubin and other compounds from the blood into the liver so that they can be cleared from the body. In Rotor syndrome, the OATP1B1 and OATP1B3 proteins are abnormally short; therefore, the bilirubin is less efficiently taken up by the liver and removed from the body, causing a buildup of bilirubin in the blood and urine which results in jaundice and dark urine [1-4]. 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 mutation which is responsible of production of truncated protein and thus causes Rotor Syndrome in our patient. This mutation was inherited from his parents. Our findings underline the impact of consanguinity of the occurrence of rare autosomal recessive diseases in populations with high consanguinity rates. In this syndrome, jaundice begins in infancy. Clinical features of Rotor Syndrome include intermittent continuing or recurrent episodes of mild jaundice. Bilirubin levels are usually in the range of 34 – 85 μmol/l, conjugated bilirubin and the results of liver enzymes are mostly normal [5]. 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[5,6]. This test not only helps in the diagnosis, but also differentiates it from Dubin-Johnson syndrome, another rare cause of benign hyperbilirubinemia [5]. The noninvasive DNA analysis is the method of choice whenever the diagnosis is unclear in subjects with suspected hereditary hyperbilirubinimia, no matter the type. Liver biopsy is not required to make the diagnosis of Rotor syndrome, but if done, liver biopsy in patients with the disease reveals normal histology. Liver biopsy may be helpful in distinguishing Rotor syndrome for other, more serious liver diseases. Since Rotor syndrome is clinically similar to Dubin-Johnson syndrome (DJS), it is imperative to distinguish between these two conditions, the absence of dark melanin-like pigments on liver biopsy distinguishes Rotor Syndrome from DJS [7-9]. Rotor syndrome is largely a diagnosis of exclusion. It is a benign disease that requires no therapy but that should be differentiated from other more serious hepatobiliary diseases. The disease is not associated with morbidity or mortality, and life expectancy is not affected [1, 8, 10].

CONCLUSION

Rotor 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.

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