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Crigler-Najjar Syndrome Type 2 in a Young Adult

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Abstract:

Crigler-Najjar syndrome type 2 in an autosomal recessive congenital non-hemolytic hyperbilirubinemia caused by UDP-glucuronosyltransferase deficiency. Only a few hundred cases have been described in the literature so far. We are reporting Crigler-Najjar syndrome type 2 in an 18 year old female born out of consanguineous marriage.

Keyword: *Crigler-Najjar syndrome, UDP-glucuronosyltransferase, Bangladesh*

Introduction:

Crigler-Najjar syndrome is an autosomal recessive congenital non-hemolytic unconjugated hyperbilirubinemia caused by UDP-glucuronosyltransferase deficiency. It has been divided into two distinct forms (types 1 and 2) based upon the severity of the disease. Type 1 disease is associated with severe jaundice and neurologic impairment due to bilirubin encephalopathy (also called kernicterus) that can result in permanent neurologic sequelae. Type 2 disease is associated with a lower serum bilirubin concentration and affected patients survive into adulthood without neurologic impairment. Crigler-Najjar syndrome type 1 was described by Crigler and Najjar in 1952 in six infants in three families.[1] The hallmark of Crigler-Najjar syndrome type 1 is pure unconjugated hyperbilirubinemia, which is usually in the range of 20 to 25 mg/dL but can be as high as 50 mg/dL. Crigler-Najjar syndrome type 2 (also known as Arias syndrome) is phenotypically similar to type 1 disease but the unconjugated hyperbilirubinemia is usually less marked; serum bilirubin is usually in the range of 8-18 mg/dL.[2] The clinical manifestations of this disorder can be illustrated by the original description by Arias in 1962 of eight patients who were between 14 and 52 years of age.[3] The phenotype of Crigler-Najjar syndrome type 1 is caused by a variety of alterations in the coding sequences of the bilirubin-uridine diphosphate glucuronosyltransferase (UGT1A1) gene which is responsible for the conjugation of bilirubin. These mutations lead to the production of an abnormal protein, resulting in complete loss or very low levels of hepatic bilirubin-UGT (UGT1A1) activity.[4] The genetic lesions in Crigler-Najjar syndrome type 2, as in type 1 disease, are located in one of the five exons that code for the bilirubin-UGT. This enzyme is totally deficient in Crigler-Najjar syndrome type 1. However, in contrast to type 1, the genetic lesions in type 2 always consist of point mutations that result in the substitution of a single amino acid which reduces but does not cause total absence of enzyme activity.[5] The residual enzyme activity is responsible for the partial conjugation of bilirubin and the lesser degree of hyperbilirubinemia. Residual bilirubin-UGT activity is about 2 to 8 percent in Crigler-Najjar syndrome type 2. The major conjugate in Crigler-Najjar syndrome type 2 is bilirubin monoglucuronide as compared to normal subjects in whom 90 percent of the conjugate is bilirubin diglucuronide.[6]

Case report:

An 18 year old lady, born out of a consanguineous marriage, was admitted in the Department of Medicine, Rajshahi Medical College with the complaints of yellow coloration sclera since 2nd week of her life. According to the statement of the patient's parents, she was well in the second week of her life. Then she developed yellow coloration of her eyes. In-charge physician of the baby assured the parents that it was normal in the newborn and advised increased exposure to sunlight. But, despite sun exposure, jaundice increased in severity up to her first month of age and then leveled off. Over next 18 years, her jaundice persisted with occasional fluctuation in severity, rising during febrile illnesses and fasting. It was not associated fever, nausea, vomiting. There was no history of itching, abdominal pain, bleeding, convulsion or muscle weakness. Her urine and stool color

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was normal .There was no history of developmental delay or intellectual impairment. She was delivered by normal vaginal delivery at home. There is no history of prolonged labor or birth asphyxia. Her parents are healthy and alive. They are first cousins. She has a younger brother who is healthy and well. On examination, she was moderately icteric; there was no hepatosplenomegaly, ascites or stigmata of chronic liver disease. Her higher psychic function, muscle power, tone and jerks were normal. On 5th April 1997, at the age of 5 years, her serum bilirubin level was 9.2 mg/dL. Conjugated and unconjugated fraction was not tested and serum ALT, AST, alkaline phosphatase levels were within normal limit. In March 2010, at the age of 18 years, her serum bilirubin level was 13.4 mg/dL; unconjugated bilirubin 12.5 mg/dl and conjugated bilirubin 0.9mg/dl. Serum ALT level: 34 U/L, serum AST level: 26 U/L and S. alkaline phosphatase level: 65 U/L. Complete blood count and blood film was normal. Reticulocyte count was 1% and Coomb's test was negative. Viral markers i.e. HBsAg, anti HCV, IgM anti HEV and IgM anti HAV were negative. MRI of upper abdomen including Magnetic Resonance Cholangio Pancreatography was reported normal. No KF ring was found on slit lamp examination of the eyes. Upper GI endoscopy with analysis of duodenal aspirate to demonstrate the presence of conjugated bilirubin could not be done because the patient refused endoscopy. Phenobarbital was started in a dose of 90 mg/day. After a week, her serum bilirubin fell to 7.5 mg/dL; unconjugated bilirubin 6.6 mg/dl, and conjugated bilirubin 0.9 mg/dl (50% reduction of unconjugated bilirubin from baseline). Liver biopsy and measurement of UDP glucoronosyl transferase in the sample, polymerase chain reaction and sequence analysis of the UDP-glucuronosyl transferase 1 A1 (UGT1A1) gene could not be done because of lack of facilities in Bangladesh.

Clinical and laboratory pattern of our patient was consistent with congenital non-hemolytic unconjugated hyperbilirubinemia. Our patient was diagnosed as a case of Crigler-Najjar syndrome by excluding other causes of unconjugated hyperbilirubinemia. History of consanguinity also supported the diagnosis. Relatively lower serum bilirubin level, survival in adulthood with no evidence of kernicterus without liver transplantation, and rapid response to phenobarbital helped us to eliminate Crigler-Najjar syndrome type 1 from differential diagnosis and to reach the diagnosis of Crigler-Najjar syndrome type 2. The patient was maintained at 60 mg of Phenobarbital per day. She was doing well when last seen.

Discussion:

Although other disorders can cause unconjugated hyperbilirubinemia in newborns, they can be distinguished based upon the level of hyperbilirubinemia and its duration. Hemolytic disorders alone do not raise serum bilirubin concentrations beyond 6 to 8 mg/dL. Physiologic jaundice usually resolves within the first 10 days of life. Serum bilirubin concentrations are usually less than 6 mg/dL in full-term neonates, and 10 to 12 mg/dL in premature neonates.[7] Breast milk jaundice is similar to neonatal jaundice except that serum bilirubin levels are higher (up to 30 mg/dL if untreated) and persist for a longer duration. They usually peak within two weeks of birth, remain elevated for 4 to 10 days, and then decline to normal over 3 to 12 weeks.[8] In Gilbert syndrome, which is also a form of congenital non-hemolytic unconjugated hyperbilirubinemia, serum bilirubin levels fluctuate; they are usually less than 3 mg/dL and can be normal. Certain associated pathologic conditions i.e. hemolysis or physiologic events i.e. fasting can increase the plasma bilirubin concentrations to higher values but usually less than 6 mg/dL.[9] In our patient, serum bilirubin level was much higher than this range. In the original report by Crigler and Najjar, who described Crigler-Najjar syndrome type 1 in six children; five of the six infants died of kernicterus by the age of 15 months. The sixth infant was free of neurologic disease until 15 years of age, when kernicterus suddenly developed; the adolescent died six months later.[1, 10] In addition, hyperbilirubinemia can be reduced by more than 25 percent during treatment with phenobarbital (60 to 120 mg for 14 days) in Crigler-Najjar syndrome type 2, which presumably works by induction of the residual bilirubin UGT activity. A response to phenobarbital is not observed in patients with type 1 disease.[11, 12] Our patient showed 50% reduction of total and unconjugated bilirubin after administration of phenobarbital. Another difference between patients with type 1 and 2 disease is the presence of bilirubin glucuronides in bile. Conjugated bilirubin is absent or present only in trace amounts in patients with type 1 who have little or no UGT1A1 activity, while a significant amount of conjugated bilirubin is detectable in the bile of patients with type 2. Thus, chromatographic analysis of bile collected from the duodenum through an orally placed duodenal catheter or an upper gastrointestinal endoscope can be used to differentiate the two forms of the syndrome.[6] We could not do this test because of patient's refusal to endoscopy. Dubin-Johnson and Rotor syndrome was excluded at the outset because they cause conjugated hyperbilirubinemia. Biliary tract pathology and viral hepatitis were also excluded by appropriate investigations.

Conclusion:

Crigler-Najjar syndrome type 2 is an extremely rare, congenital non-hemolytic unconjugated hyperbilirubinemia caused by deficiency of UDP-glucuronosyltransferase. In contrast to type 1 Crigler-Najjar syndrome type, type 2 patients survive into adulthood and usually do not develop kernicterus. Early diagnosis, phenobarbital therapy and genetic counseling are quite useful in managing patients with Crigler-Najjar syndrome type 2.

Conflict of Interest: None

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