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Case Report

Effects of high bilirubin level in pregnancy in Crigler–Najjar syndrome type 2: An extremely rare but important clinical entity to recognize

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ABSTRACT

Crigler–Najjar is a rare genetic autosomal recessive disorder caused by deficiency of enzyme Uridine 5-Diphosphate Glucuronosyl Transferase (UDP-GT). We report the case of a 24-year-old female with two consecutive pregnancies with a high level of total bilirubin level of 15.1 mg/dl and a direct bilirubin level of 0.8 mg/dl during the first pregnancy. As she was diagnosed case of Crigler Najjar type 2, she was on phenobarbitone 60 mg daily. With careful monitoring, she continued with the same dose. We concluded that even with high bilirubin level (15.1 mg/dl) in pregnancy, no adverse effects to the baby and mother were seen.

Introduction

Crigler–Najjar syndrome (CNS) is a rare autosomal recessive condition caused by complete (type I) or incomplete deficiency (type II) of hepatic microsomal enzyme uridine 5-diphosphate glucuronosyltransferase (UDP-GT) activity.[1,2] The gene coding for UDP-GT, UGT1A1, has been mapped to 2q37, and mutations associated with both type I and type II have been reported.[3–5]

Crigler–Najjar type 1 (CN-1) was first described in 1952, and its prevalence is 0.6–1 per million, characterized by striking unconjugated hyperbilirubinemia with no detectable constitutive expression of UGT1A1 activity in hepatic tissue.[6] Infants have high unconjugated bilirubin levels in the range of 20–45 mg % and usually die within the first year of life due to kernicterus. In CN-1, the stools are pale. Type I disorder shows an autosomal recessive inheritance pattern.

Crigler–Najjar type 2 (CN-2) is a rare condition with an incidence of 1 per 1,000,000 births.[7] Crigler–Najjar type 2 differs from Crigler–Najjar type 1 in several ways like bilirubin concentration is low 6–25 mg% (usually ≤20), infrequently associated with kernicterus, bile is deeply colored, and bilirubin glucuronides are present with a characteristic increase in the proportion of monoglucuronides, UGT1A1 (UDP glucuronosyltransferase 1-A1) in the liver is usually present at a reduced level (typically ≤10% of normal) and treatment with phenobarbitone decreases bilirubin by >25%.

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Age of presentation is the first year of life but can also present in the third decade. It mainly presents with jaundice. The rise in bilirubin levels can occur during fasting or illness. Levels of bilirubin can be elevated due to the stress of pregnancy. The placenta is an ineffective barrier for unconjugated bilirubin and can result in high bilirubin levels in the neonate causing kernicterus and sometimes even death.[8]

We hereby report a case of CN type 2 in a pregnant female with a bilirubin level above the recommended cut-off value (<10 mg/dl) and her successful pregnancy outcome.

Case report

A 24-year-old female patient with P2L2A0 with diagnosed case of Crigler–Najjar syndrome type 2 since childhood by TATA box sequencing that was negative for gilbert syndrome and phenobarbitone test was positive. The patient had been counseled for the same. She was started on phenobarbitone 30–150 mg daily according to bilirubin level. She came to our hospital with a history of 12 weeks of amenorrhea with an increase in yellowish discoloration of the eye. She had no complaints of abdominal pain, nausea, vomiting, bleeding manifestations, altered sleep cycle, and itching. She had no history of blood transfusion. Her family history revealed that her younger brother also had similar complaints of jaundice since birth (Fig. 1). He was also diagnosed with Crigler–Najjar type 2 since birth. No history of consanguineous marriage in the family. No history of jaundice in parents. Her vitals were within normal limits. Systemic examination was also within normal limits. Her hemoglobin was 9.2 gm/dl; platelets counts 1.7lac/mm^3, liver enzymes and LDH were in the normal range. Peripheral blood smear showed no signs of hemolysis. Total bilirubin was 15.1 mg/dl (Fig. 2) and direct bilirubin was 0.8 mg/dl and serum albumin was 4.3 gm/dl with bilirubin-albumin ratio was 3.5. Her viral markers, Wilson disease serology, and autoimmune workup were negative. Her USG abdomen reveals no significant abnormality. She was continued on phenobarbitone 60 mg without any dose modification. Her total bilirubin was 11.3 mg/dl, and direct bilirubin was 0.8 mg/dl at full-term delivery. The baby was born by normal vaginal delivery with a weight of 3.2 kg, and total bilirubin was 3.8 mg/dl, and indirect bilirubin was 3.2 mg/dl. The baby was put on phototherapy for 3 days. Serum bilirubin was 0.8 mg/dl at day 4 (Fig. 3). The newborn examination was within normal limits (APGAR score at 1 min and 5 min was 9).

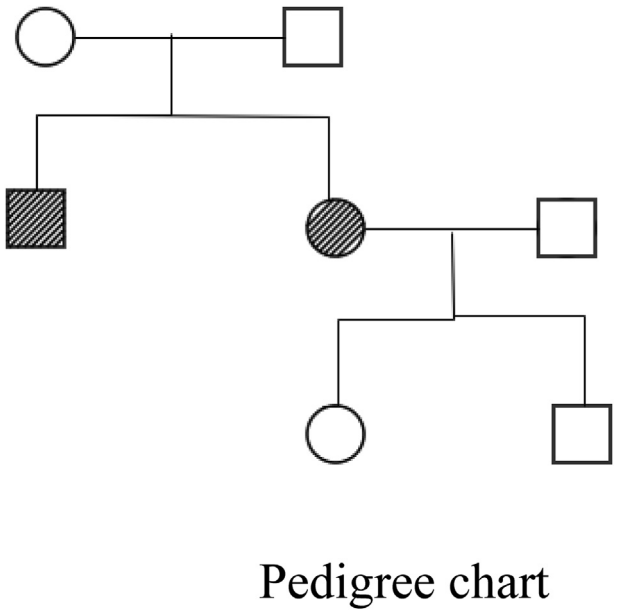

Fig. 1 – Pedigree of family with Crigler-Najjar syndrome type II.

During the second pregnancy, she had total bilirubin 6.8 mg/dl and indirect bilirubin 5.8 mg/dl. She was continued on phenobarbitone 60 mg per day. The second delivery was also normal vaginal delivery with no complications to the mother and newborn. Currently, both children (2-year-old and 1-year-old boys) are normally developed, and their serum bilirubin levels are also within normal limits. Patient consent was obtained before entry into study.

Discussion

Crigler–Najjar syndrome is a rare autosomal recessive disorder of bilirubin metabolism with an incidence of 1 in 750,000–1,000,000, affects males and females in equal numbers. Type 1 Crigler–Najjar in which jaundice is severe, leads to kernicterus in the newborn, while type 2 Crigler–Najjar is associated with a lower level of bilirubin and responds to phenobarbitone treatment.

In the present case report with Crigler–Najjar type 2, serum bilirubin was increased to above 10 mg/dl in pregnancy; in spite of that, the pregnancy outcome was uneventful as opposed to many previous case reports of adverse effects to pregnancy when serum bilirubin level goes above 10 mg/dl. So it suggests that even after raised serum bilirubin above the recommended level, pregnancy can be continued with watchful expectant management.

Chaubal et al observed that maternal serum bilirubin levels should be below 10 mg/dl during pregnancy.[9] Adverse neonatal outcomes have been reported with untreated CN type 2 with high maternal serum bilirubin (17.0–21.8 mg/dl), manifesting as neonatal quadriplegia but in our case, despite serum bilirubin rising above 10 mg/dl had a favorable outcome.

In a study by Pinkee *et al*[10] it was shown that a maternal bilirubin of 10.8 mg/dl at delivery required treatment with exchange transfusions and phototherapy.[10] We continued phenobarbitone 60 mg once daily at a serum bilirubin level of 15.1 mg/dl, and at delivery, serum bilirubin was 11.3 mg/dl without exchange transfusion and phototherapy with close monitoring. We were able to restrict the fetal morbidity and mortality in our case report.

Maternal serum bilirubin levels should be kept below 8–10 mg/dl.[11] In Crigler–Najjar type II pregnant patients, phenobarbitone treatment seems to be a safe option, and neurologic follow-up, including sensitive hearing tests of these children, is strongly recommended, as hearing disorders are among the commonest sequelae of kernicterus, and although well treatable, are frequently underdiagnosed.

There are several studies regarding placental bilirubin metabolism. Unconjugated bilirubin crosses the placental

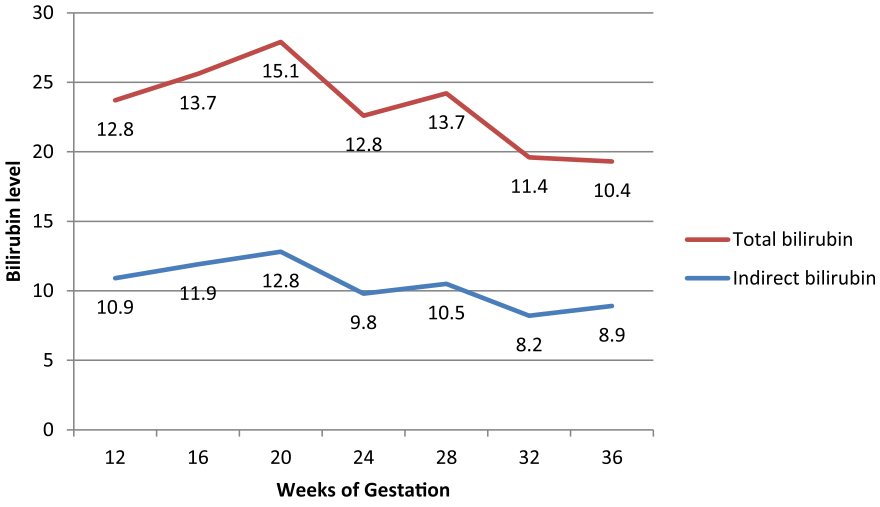

Fig. 2 – Relationship of weeks of gestation with bilirubin level.

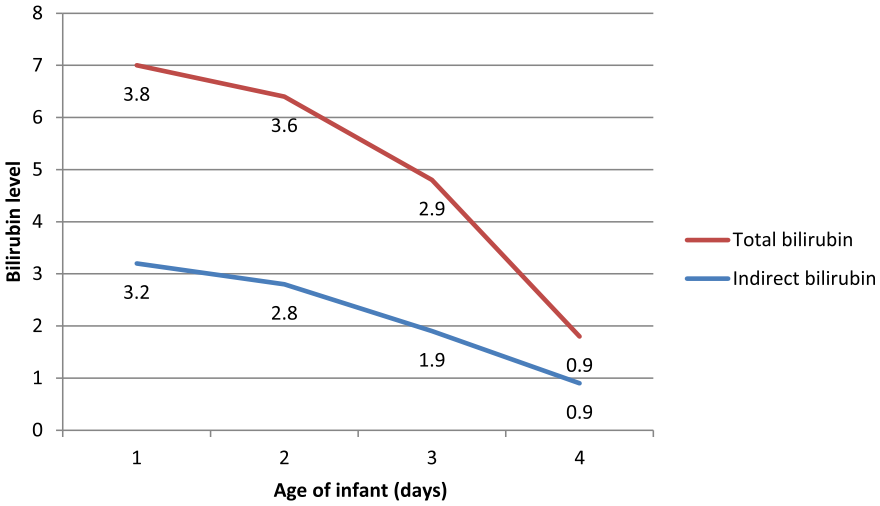

Fig. 3 – Relationship of age of infant with bilirubin level.

barrier to cause high levels of bilirubin in the fetus resulting in neurological damage (kernicterus) or even death.[12] It seems reasonable to try to keep the maternal (and therefore the fetal) unconjugated bilirubin concentrations below 200 mmol/l (11.7 mg/dl).[11,13]

Treatment of CN type 2 is usually conservative with avoidance of drugs that displace bilirubin from albumins like penicillin, sulphonamides, salicylates, ceftriaxone, and furosemide.[14]

It is unclear at which bilirubin level kernicterus will develop regarding the accepted level of unconjugated bilirubin in pregnancy. Studies so far referred to neonates, but the objective of intrauterine tolerance to bilirubin has not been addressed yet. It is generally accepted that premature and sick neonates are more susceptible to hyperbilirubinemia than mature neonates. We, therefore, monitored bilirubin levels closely and fetal well-being. In our case, we were able to manage pregnancy even at higher bilirubin levels with expectant management and with a good outcome for mother and baby. However, neurological follow-up should be carried out for newborns, which includes hearing disorders during early childhood.

Disclosure of competing interest

The authors have none to declare.

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