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Case Report

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Management of a pregnancy with Crigler-Najjar syndrome type 2: a case report

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Abstract

Objective: To report a case with Crigler-Najjar syndrome type 2 of elevated bilirubin levels who was treated with triple therapy.

Case: Crigler-Najjar syndrome is a rare congenital disorder that causes non-obstructive non-hemolytic unconjugated jaundice. The syndrome is divided into two groups according to the severity and the clinical presentation of the disease. In these cases, there is an elevated risk of antenatal death or permanent neurological impairment of the fetus due to fetal kernicterus caused by excessively increased unconjugated bilirubin levels. Phototherapy, phenobarbital and plasmapheresis can be useful in reducing serum total bilirubin concentrations, thus adverse maternal and neonatal risks.

Conclusion: At her 37 weeks of gestation, the patient delivered a healthy girl. No pathological neurological findings were found and the baby had normal growth with intact neurological development.

Keywords: Crigler-Najjar syndrome, jaundice, hyperbilirubinemia.

Introduction

Crigler-Najjar syndrome (CNS) is a rare congenital disorder associated with the complete absence or reduction in the activity of the uridine diphosphate glucuronosyl transferase enzyme. It is an autosomal recessive condition that has an incidence of less than one in a million births.[1] Crigler-Najjar syndrome is divided into two groups according to the severity and the clinical presentation of the disease and the response to phenobarbital therapy. In Type 1 CNS, which was first described by Crigler and Najjar in 1952, the pathology was the complete absence of the enzyme activity.[2] In these cases, there is an elevated risk of antenatal death or permanent neurological impairment of the fetus due to fetal kernicterus caused by excessively increased unconjugated bilirubin levels.[3] Type 2 CNS was first described by Arias in 1962.[4] In type 2 disease, the clinical presentation is less severe with a reduced level of enzyme activity. Affected patients generally survive into adulthood without any neurological sequelae and they respond well to phenobarbital treatment.[5]

Pregnancy in CNS patients is a challenge because of the risk of fetal kernicterus and rising bilirubin levels of the mother, who is exposed to the stress of pregnancy. Placental passage of indirect bilirubin during pregnancy can lead to permanent neurological impairment because of high bilirubin levels in the newborn. Therefore, morbidity and mortality in newborns can be prevented with early diagnosis and treatment.

In this study, we presented a case of Crigler-Najjar syndrome type 2, and the follow-up and treatment

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approaches during pregnancy and the neurological evaluation of the newborn in line with the literature.

Case

A 24-year-old female patient, with known Crigler-Najjar syndrome type 2, had maintained her bilirubin levels around 12–13 mg/dL with a phenobarbital treatment of 200 mg. She was admitted to the outpatient clinic at 5 weeks of gestation, to investigate the probable risks of phenobarbital use during pregnancy, which she stopped taking upon learning of her pregnancy. She had a total bilirubin level of 18.3 mg/dL and a conjugated bilirubin level of 0.84 mg/dL. Physical examination showed distinctly icteric sclera and skin. In family history, we learned that the patient's parents had a consanguineous marriage (cousins).

At 11 weeks of gestation, the patient's total bilirubin level was 25.4 mg/dL and the conjugated bilirubin level was 0.86 mg/dL. The patient was consulted to Hematology and Gastroenterology Clinic. The treatment plan was to follow the patient with phototherapy, phenobarbital and plasmapheresis (albumin) until delivery. The patient received plasmapheresis treatment starting at 13 weeks and 3 days of the gestation until delivery, two days a week. A permanent central venous catheter was placed for plasmapheresis at the 15 weeks of gestation. Her bilirubin levels were measured, and phototherapy was performed every day. The patient's average value of total bilirubin during pregnancy was 17.7 mg/dl. **Figs. 1** and **2** show the changes in the patient's total and direct bilirubin levels during pregnancy and subsequent follow-ups, respectively.

Because of her elevated bilirubin levels, it was considered that the use of phenobarbital was a clinical necessity. The patient was informed about the risks of phenobarbital drug use, which has a pregnancy category of group D, in the first trimester of pregnancy. The patient requested the continuation of the pregnancy but refused phenobarbital treatment until the second trimester. Upon the patient's request, daily 60 mg of phenobarbital treatment was started after the 16 weeks of gestation.

At 16 weeks of gestation, abdominal ultrasound was performed due to abdominal pain complaints and millimetric stones in the gallbladder were observed. When a signal change compatible with the stone was observed in MRCP, an ERCP was performed, and the stone was removed. She was managed with IV hydration, and ceftriaxone and metronidazole treatment were administered for 10 days, at the end of which the patient's complaints regressed.

Measurements made in fetal biometrics in routine pregnancy follow-ups were found to be consistent with her gestational age, and no increase in resistance was found in the umbilical artery. Second-trimester ultrasonography was performed at 20 weeks of gestation and showed normal fetal growth with no fetal abnormalities with a posterior placenta and adequate amniotic fluid.

At 37 weeks, the patient was admitted due to contractions with a total bilirubin level of 11.8 mg/dL, and conjugated bilirubin level of 0.60 mg/dL. A primary cesarean delivery was performed and the patient gave birth to a healthy girl weighing 2510 g with Apgar 9/9. The baby needed 5 minutes of CPAP in the delivery room. The patient was discharged on the second postop day without any complications, and the baby was admitted to the neonatal ward due to hyperbilirubinemia (total bilirubin: 10.9, direct bilirubin: 1.20) and received phototherapy and transfusion. In the examination of the baby, no pathological neurological findings were found and neonatal reflexes were evaluated normal. **Figs. 3** and **4** show the total and direct bilirubin levels during the follow-up of the baby. Newborn hearing screening tests (otoacoustic emission), as well as the brainstem auditory evoked potential performed at 1 month of age were normal. Cranial MRI results were reported normal. The baby was followed up during her first year of life and had normal growth with intact neurological development.

Discussion

Crigler-Najjar syndrome, which can be defined as congenital non-obstructive non-hemolytic unconjugated jaundice is caused by the mutations in the UDPGT gene (Exon 1×1.5).[6] Maternal unconjugated bilirubin levels rise because of the stress caused by pregnancy, and maternal bilirubin passes the placenta with passive diffusion. Studies show that the placenta is not a barrier for the unconjugated bilirubin entering the fetal circulation[7] and that the bilirubin levels of the newborn are similar to those of the mother.[1] The fetal hyperbiliru-

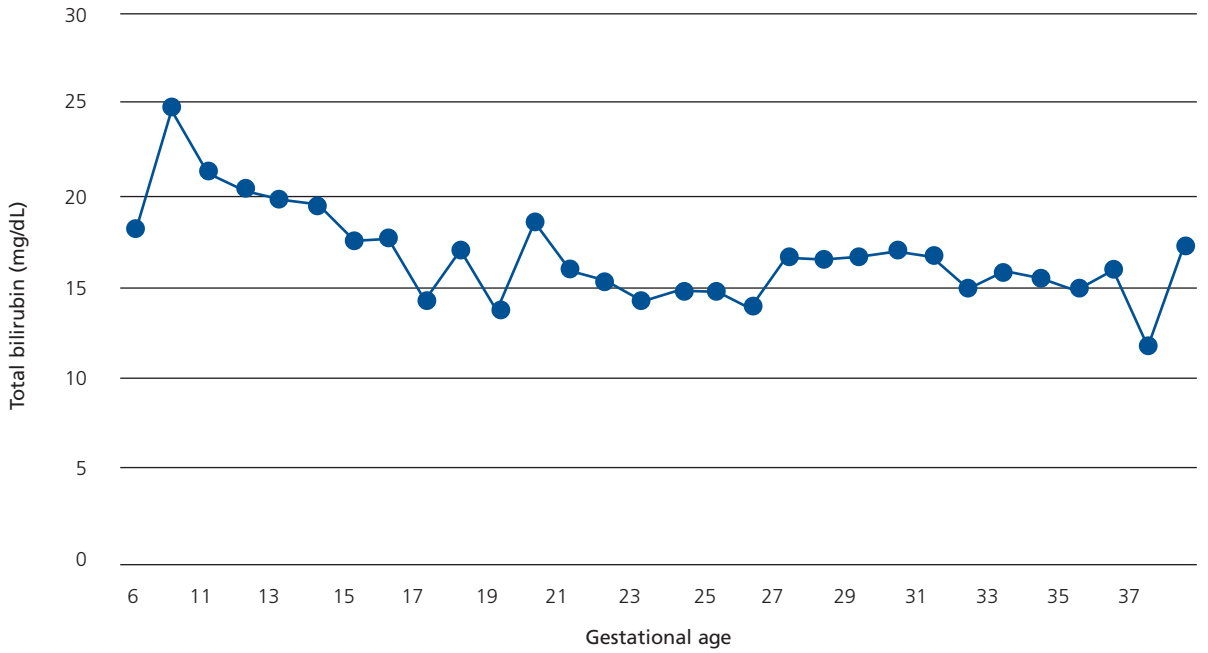

Fig. 1. Changes in the patient's total bilirubin levels.

binemia caused by this maternally-induced bilirubin may result in permanent neurological impairment in the fetus (plegia, ataxia, deafness, spasticity, mental retardation, seizures and death). These complications are more common in type 1 and untreated type 2 CNS patients.[8] In this study, similar to the previous studies, the serum total bilirubin level of the newborn was similar to that of the mother during delivery.

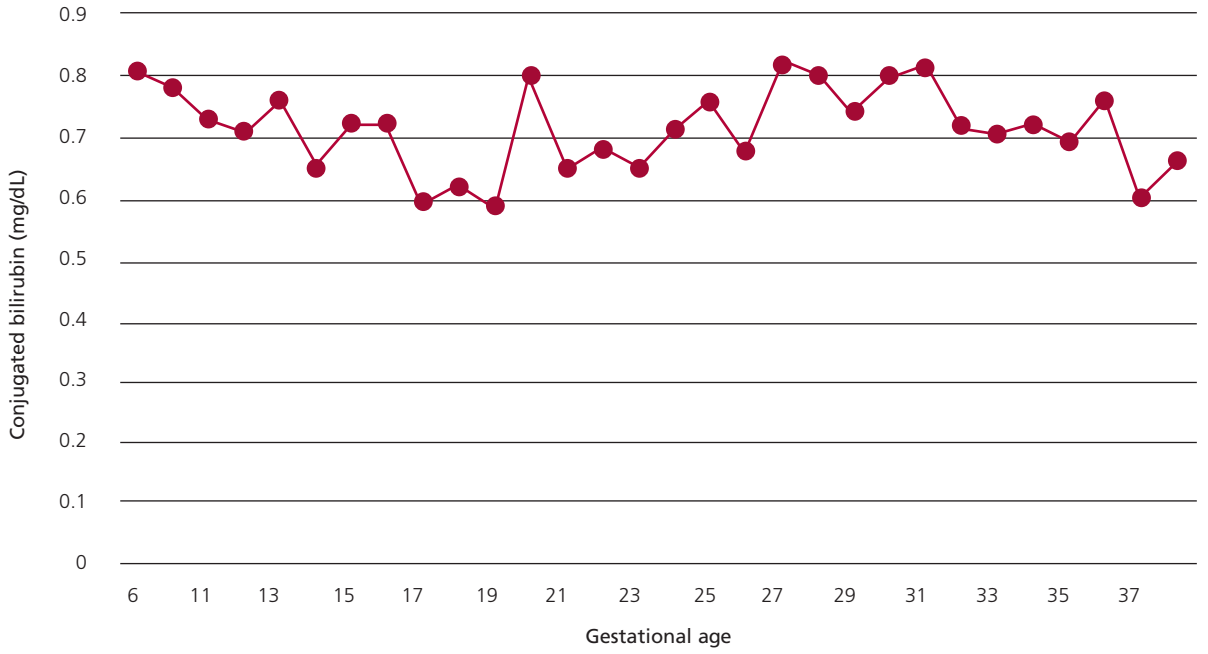

Fig. 2. Changes in the patient's direct bilirubin levels.

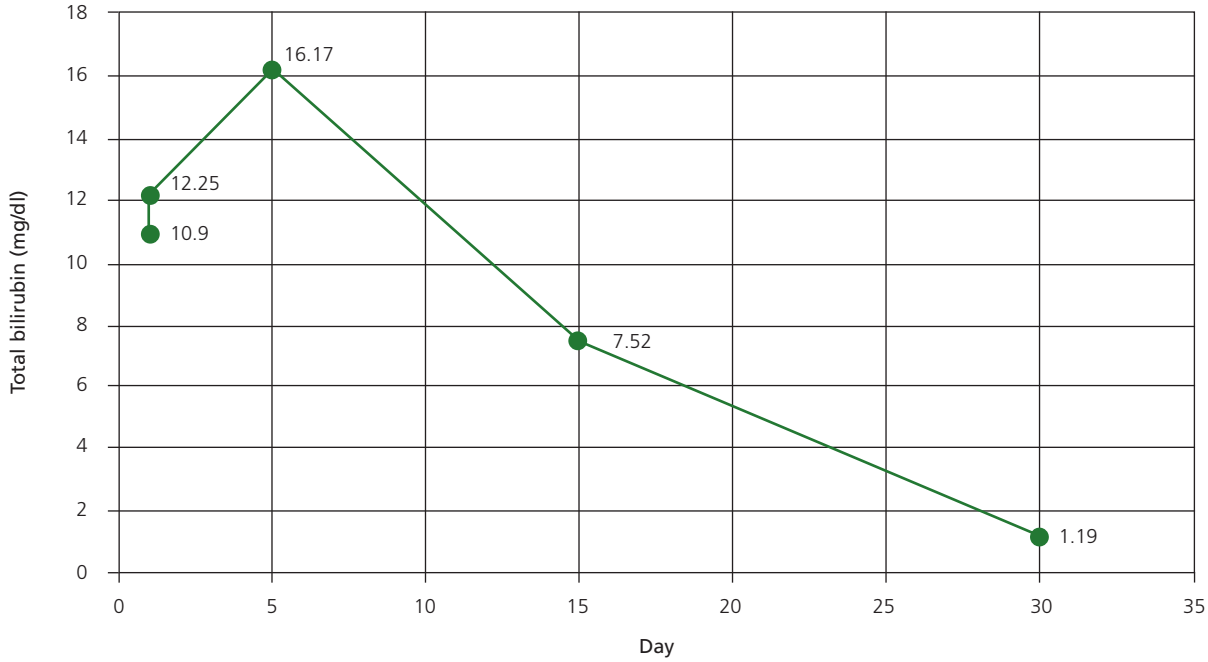

Fig. 3. Total bilirubin levels of the newborn.

There is no consensus in the literature about the precise level of serum bilirubin that causes permanent damage to the developing fetal nervous system.[9] The mechanism of how unconjugated bilirubin causes neurotoxicity is also not known.[10] However, some authors argue that levels of <10 mg/dl are safe,[6,11]

In their study, Holstein et al. maintained the maternal serum total bilirubin levels between 4.2 and 8.9

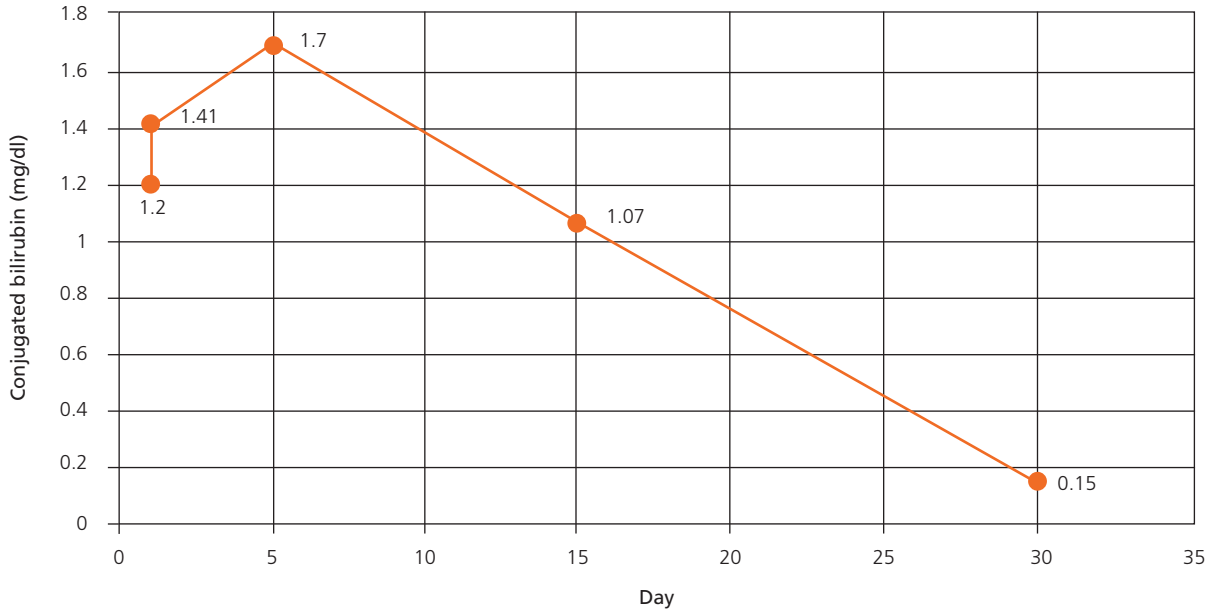

Fig. 4. Direct bilirubin levels of the newborn.

mg/dl by phenobarbital and phototherapy, and the pregnancy resulted in the birth of a healthy newborn.[12] In a case reported by Cahill et al.,[13] the mother was administered 60 mg/d of phenobarbital, the total bilirubin level of the mother was kept between 5.0 and 5.1 mg/dl during pregnancy, the baby was born without any complications and developmental delay was not detected during growth. Taylor et al.[14] reported a case in which the serum total bilirubin concentrations of the mother ranged between 17.0 and 21.8 mg/dl during pregnancy. Following a grand mal seizure that developed in the mother who had not received any treatment for CNS, a male infant was born by cesarean section. The baby was markedly icteric at birth and the total bilirubin concentration was 19.5 mg/dl. Despite a good response to phototherapy, the infant developed quadriplegia. In the case reported in this study, despite the relatively higher bilirubin levels, the outcome is compatible with previous studies. The pregnancy resulted in a normal infant at birth with no neurological impairment.

Especially in cases with type 2 Crigler-Najjar syndrome, decreasing the maternal unconjugated bilirubin levels may prevent kernicterus development during pregnancy and after birth.[5] Phototherapy and phenobarbital are useful for reducing serum total bilirubin concentrations. Phototherapy causes a rapid decrease in total bilirubin levels, while phenobarbital keeps bilirubin levels at this level. Concomitant use of phototherapy and phenobarbital in a patient with type 2 Crigler-Najjar syndrome was first described by Ito et al. in 2001.[5] Phenobarbital has been classified as pregnancy category D and the drug causes fetal facial dysmorphism and mental retardation. Nevertheless, these risks occur at very high doses (750–1500 mg/d), and such an effect was not shown at doses of 60 mg/dl.[15] In the case reported in this study, triple use of phototherapy, plasmapheresis and phenobarbital were recommended to the patient due to high maternal serum bilirubin levels at the 11 weeks of gestation. However, the patient refused to use phenobarbital until the second trimester of the pregnancy. Phototherapy and plasmapheresis were administered to the patient until the 16 weeks of gestation, followed by triple therapy including low-dose phenobarbital and the treatment continued throughout the pregnancy.

There is no indication for treatment in the baby of a mother with Crigler-Najjar syndrome who was not born with jaundice. Treatment is indicated in term infants with serum bilirubin levels above 10 mg/dl, while bilirubin levels of more than 4 mg/dl are an indicator for phototherapy in infants with high risk of kernicterus (preterm labor, low birth weight, etc.).[6] In this study, we observed the serum total bilirubin level at birth 10.9 mg/dl and applied phototherapy to the newborn.

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