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Case Report

Maternal outcome of Crigler-Najjar syndrome type-2: Case report

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ABSTRACT

Crigler-Najjar Syndrome type 2 [CN-2] is an uncommon inherited disorder characterized by non-hemolytic unconjugated hyperbilirubinemia. It is caused by mutations in one of the five exons of the UGT1A1 gene which codes for the enzyme hepatic uridine diphosphate glucoronosyl transferase-1, required for the conjugation and further excretion of bilirubin from the body via bile. Affected people are usually asymptomatic apart from jaundice and investigations reveal isolated indirect hyperbilirubinemia. It can be conveniently diagnosed by evaluating the response to phenobarbital in terms of reduction in bilirubin levels. Genetic testing confirms the finding of Crigler-Najjar syndrome. At least 20 different mutations of UGT1A1 have been associated with CN-2; all encode a bilirubin-uridine diphosphate glucuronosyl transferase-1 with markedly reduced but detectable enzymatic activity. Bilirubin concentrations are typically lower in CN-2, and plasma bilirubin levels can be reduced to 3 to 5 mg/dL by phenobarbital. Although uncommon in CN-2, bilirubin encephalopathy has occurred at all ages, typically associated with factors that temporarily elevation the plasma bilirubin concentration above baseline e.g. stress, prolonged fasting, an intercurrent illness like influenza. For this reason, phenobarbital therapy is often recommended. CN-2 is infrequent, and only a few pregnancies with this condition have been reported. The objective of the case study is to report a rare case of maternal CN-2 in the pregnancy and to evaluate whether pregnancy is safe in patients with the disease. A 29 years old mother with CN-2 had given birth to a baby girl by spontaneous vaginal delivery without complications. The newborn had mild unconjugated hyperbilirubinemia which was further treated by phototherapy and early morning sunlight. It can be concluded that that pregnancy need not be contraindicated in CN-2.

1. Introduction

Three variants of genetic polymorphisms in the glucuronidation of bilirubin have been described. Two of these inborn errors in metabolism [Crigler–Najjar syndromes 1 and 2] can be fatal while the third [Gilbert's syndrome] is less serious.[1,2] In CN-1, there is a complete absence of hepatic UDP-glucuronosyltransferase-1 activity, whereas patients with CN-2 have up to 10% of normal and patients with Gilbert's syndrome have 10 to 30% of normal, leading to bilirubin concentrations of 18 to 45, 6 to 25, and 1.5 to 4 mg/dL, respectively. Patients with CN-1 and CN-2 are either homozygotes or double heterozygotes for structural mutations within the coding region.[3] CN-2 is inherited as an autosomal recessive disease, although occasional patients with autosomal dominant inheritance have been reported.[4] CN-2 appears to be a milder variant of type I and is characterized by unconjugated hyperbilirubinemia. The deficiency of bilirubin UDP-glucuronosyl transferase is less severe, but the mechanism of this difference is not entirely clear.[5] During intercurrent illness, general anesthesia, or prolonged fasting, bilirubin levels could be as high as 40 mg/dL. Bilirubin encephalopathy is unusual in this group but can be precipitated during incidents of exacerbated hyperbilirubinemia. As in CN type 1, there is no evidence

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of hemolysis or other hepatic dysfunction. CN-2 is clinically differentiated from type-1 by >25% reduction of serum bilirubin after administration of enzyme-inducing agents e.g. phenobarbital and the presence of a significant concentration of bilirubin glucuronides in bile although the proportion of bilirubin monoglucuronide exceeds 30% of total conjugated bilirubin normal, ~10%, reflecting a reduced hepatic UGT1A1 activity. The liver histology is normal, and UGT1A1 activity is usually reduced to approximately 10% of normal.[6]

Crigler-Najjar syndrome type-2 [also known as Arias disease] is more common than type-1 and is typically benign. Evidence of hemolytic disease is absent [although it may occur coincidentally], and neonates are otherwise healthy as summarized in table-1. Jaundiced neonates respond readily to oral administration of phenobarbital along with phototherapy with a sharp decline in serum bilirubin concentrations, whereas individuals with type-1 disease demonstrate no such change.[4] Maternal CN-2 is a rare condition and slight is known about the effects of the condition on the mother and her fetus/newborn. We present the pregnancy of a CN-2 maternal patient, pregnancy management, and the favorable outcome associated with this condition.

2. Case Report

Vaishali was a 29 years old female of Indian origin who first presented at the neonatal stage with an unconjugated hyperbilirubinemia up to 14 mg/dL without hemolytic anemia. The patient was diagnosed with CN-2 soon after delivery at the age of 9 months. The patient was the third kid of non-consanguineous parents. There was no history of congenital abnormalities, mental retardation, neonatal/infant death, or neurological disorders in their families. The patient periodically went through phenobarbital treatment for the reduction of bilirubin levels associated with jaundice; the mean bilirubin levels achieved as the result of these treatments were around 7 mg/dL. The patient had complaints like frequent nausea, headache, fatigue, yellow discoloration of sclera, high colored urine, and vertigo since childhood. Some of these complaints were managed by homeopathy treatment. Apart from that she was healthy, had no neurological abnormalities, and had a university degree. The patient's blood group was B Rh-ve and the husband's blood group was B Rh+ve. The husband had a normal bilirubin levels and no family history of jaundice as well as Crigler–Najjar syndrome. The patient's bilirubin levels were stable at around 10-14 mg/dL and never went below 7 mg/dL. Her gynecologist and hepatologist decided to stop phenobarbital therapy completely to reduce the risk of drug dependence as well as embryopathy. They advised taking a high protein diet, protein powder, and liver tonic. DNA analysis of the UGT1A1 gene polymorphism showed that the patient had a 7/7 heterozygous UDT1A1*28/*28 allele with 7TA repeats mutations. Additionally, she was found to carry the 2 alleles with 7 TA repeat polymorphism. The couple was counseled by a hepatologist regarding the pregnancy outcome.

In the first unplanned pregnancy, first-trimester screening showed normal nuchal translucency 1.6 mm. The patient's body weight was 44kg. The thyroid function test and liver enzyme level SGPT were reported as normal. The indirect bilirubin level was reported 8 mg/dL. Hemoglobin level was 13gm%. Australia antigen test HbsAg for viral hepatitis B and HIV antibody test was negative and non-reactive. Detailed anomaly ultrasound sonography done at 19/6 weeks gestation and repeated during the third trimester of pregnancy showed no detectable fetal abnormalities, normal liver with no biliary obstruction and raised serum bilirubin with liver function tests. Her liver function tests were repeated after regular intervals during pregnancy. The patient was continued with oral hematinic, calcium, multivitamins, and protein supplements. The patient was admitted to the maternity hospital and labor induced at 40.1weeks' gestation. The patient's body weight was 55kg and unconjugated bilirubin was 7.4 mg/dL see figure-1. Delivery was spontaneous, vaginal, and uncomplicated at 40.2 weeks gestation and resulted in a newborn girl with mild unconjugated hyperlipidemia. The newborn baby's total bilirubin was 6.0 mg/dL mild hyperbilirubinemia and hemoglobin count was 14.4gm% on the first day. Baby's birth weight was 3320gm and blood group ORh+ve. No congenital abnormalities were detected on the newborn's physical examination apart from mild unconjugated hyperbilirubinemia. The baby was kept under phototherapy from first day with medical supervision. The baby's reticulocyte count was normal 5.38% and the direct Coombs test used to test for autoimmune hemolytic anemia was negative. The patient started breastfeeding to baby on the third day after delivery. The maternal and newborn bilirubin levels were monitored. The phototherapy was continued up to 5 days but still total bilirubin level was 8.2 mg/dL. The patient was discharged from the hospital on the sixth day and the pediatric physician advised for morning sunlight to the baby every day. Total bilirubin level was found normal after one month was normal which was monitor for 3 months refer Figure 2. Hearing studies, as well as brainstem auditory evoked potential performed at 3 months of age were normal.[7]

3. Discussion

Crigler-Najjar syndrome may possibly be identified easily within a few days after birth as the newborn is jaundiced. Further, for the confirmation of diagnosis, clinical evaluation could be extended to genetic analysis, hematological testing, liver function test and probing the family history. The prevalence of CN-2 is not known but an approximate annual incidence of 1 per million live births

Table 1: Reports of maternal outcome of Crigler-Najjar syndrome type 2 in the literature

	Maternal bilirubin at delivery mg/dL	Maternal treatment	Mode of delivery	Newborn treatment	Fetal outcome
Hunter et al., 1973 [8]	9.5-13.8	phenobarbital	spontaneous vaginal	phototherapy, phenobarbital	normal
Labrune et al.,1989 [9]	not available	not available	not available	none	abnormal
Labrune et al.,1989 [9]	not available	not available	not available	phenobarbital	normal
Cahill et al., 1989 [10]	11–13	phenobarbital	Induced	phototherapy	normal
Smith et al., 1994 [11]	5.3–9.6	none	spontaneous vaginal	none	normal
Ito et al., 2001 [12]	75–173	phototherapy, phenobarbital	caesarean	none	normal
Holstein et al., 2005 [13]	4.2–8.9	phototherapy, phenobarbital	caesarean	none	normal
Pinkee et al., 2005 [14]	10-11	none	spontaneous vaginal	phototherapy, blood transfusion, phenobarbital	normal
Saxena 2005 [15]	6-8	none	spontaneous vaginal	none	normal
Saxena 2005 [15]	7-9	none	spontaneous vaginal	phototherapy, blood transfusion, phenobarbital	normal
Passuello et al 2009 [16]	4–8.5	phenobarbital	spontaneous vaginal	none	normal
Arora 2009 [17]	5-7	none	spontaneous vaginal	phototherapy	normal
Holstein et al., 2010 [18]	4–6	phototherapy, phenobarbital	caesarean	none	normal
Chaves 2011 [19]	11-12	phototherapy	spontaneous vaginal	phototherapy	normal
Chaves 2011 [19]	8-10	phototherapy	Induced	phototherapy	normal
Shakuntala et al., 2012 [20]	8-9	phenobarbital	spontaneous vaginal	phototherapy	normal
Sagili et al., 2012 [21]	10-14	phenobarbital	caesarean	phototherapy	normal
Chaudhary et al., 2014 [22]	9.7-10.2	none	caesarean	none	normal
Chaubal et al., 2016 [23]	8-10	phenobarbital	spontaneous vaginal	none	normal
Khandelwal et al., 2018 [24]	18-20	phenobarbital	spontaneous vaginal	none	normal
Deore, 2021 present case	8-9	none	spontaneous vaginal	phototherapy	normal

has been found in case reports from worldwide for both the types of CNS.[25] The patient under the case study was a rare case of CN-2 where serum bilirubin usually had not been exceeded 10 mg/dL. We had monitored the patient's bilirubin levels, serum albumin and liver enzymes at bimonthly intervals. The patient had been remained untreated for hyperbilirubinaemia. Figure 1 reflects the maternal bilirubin level during the entire gestational age. In pregnancy, the placental crossing of unconjugated bilirubin can cause hyperbilirubinemia in the fetus with low UDT-glucuronosyl transferase-1 activity. This may lead to permanent neurological complications such as hearing problems, mental retardation, and choreoathetosis in the newborn.[26,27] Therefore, due to the high risk associated with preterm birth and maternal CN-2, the baby was immediately transferred to the neonatal intensive care unit. Figure 2 reflects the serial serum total bilirubin levels measured in the baby. At 4 hours and 24 hours of birth total bilirubin levels were 6.0 mg/dL and 8.2 mg/dL even with the commencement of phototherapy from 4 hours

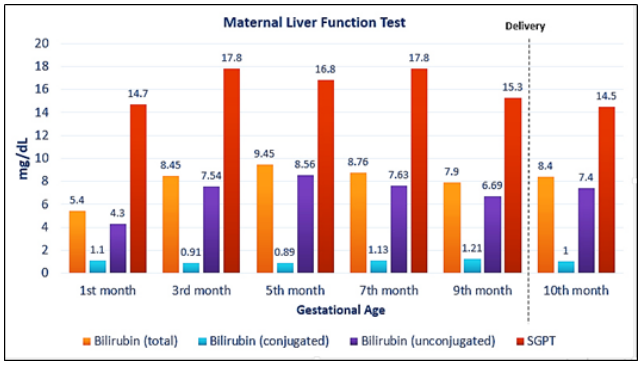

Fig. 1: Maternal liver function test during gestational age

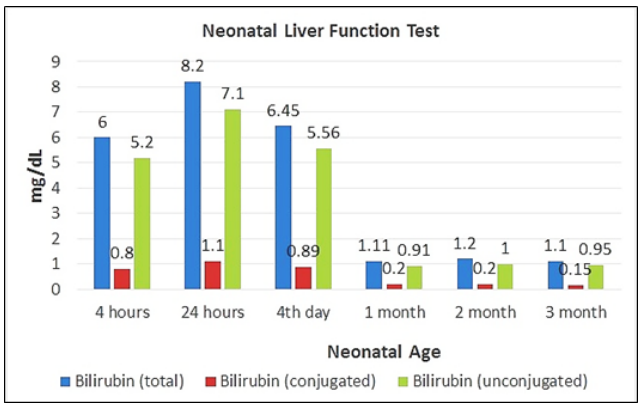

Fig. 2: Neonatal liver function test

after birth. The pediatric physician advised giving morning sunbath to the baby to get complete recovery from neonatal jaundice.[28,29] The success of phototherapy depends on photochemical alterations of bilirubin within light-exposed tissues. These reactions modify the structure of bilirubin to convert into water soluble form to be removed via renal as well as biliary excretion.[30]

We report this case due to its infrequency. The literature and reported studies reveal only 20 pregnancies from 17 maternal CN-2 patients worldwide. Reports of the maternal outcome of CN-2 in the literature as summarized in table-1. Data suggest that pregnancy need not be contraindicated in CN-2.[23] But quick identification and interdisciplinary connection of pediatrician, gynecologist, hematologist, hepatologist, blood bank officer and laboratory technician in these high-risk pregnancies we can achieve optimal maternal and fetal outcome.

Currently, research on inborn errors of metabolism is a hot topic. Scientists are destined to develop enzyme replacement therapies that may complement the deficient or missing enzyme. Research is also ongoing on whether liver transplantation could help patients in this regard, because although the liver remains normal in these patients, transplantation could correct the malfunctioning hepatocytes and provide normal UGT1A1 enzyme.

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5. Conflict of Interest

None.

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