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Crigler-Najjar Syndrome Type 2 in Pregnancy: A Rare Case Report

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Abstract
Crigler-Najjar syndrome is a rare autosomal recessive condition caused by complete (type I) or incomplete deficiency (type II) of hepatic microsomal enzyme uridine diphosphate-glucuronosyltransferase (UDPGT) activity. It is characterized by congenital unconjugated hyperbilirubinemia1-2. It is caused by mutations in the UGT1A1 gene which codes for the enzyme uridine diphosphate glucoronosyl transferase- 1, required for the conjugation and further excretion of bilirubin from the body.
Objectives: *Our objective in report this case is to know the outome of pregnancy in patient with crigler-Najjar syndrome type 2.*
Case: *A 25 year old primigravida woman was admitted to our hospital with history of amenorrhoea for 9 months and history of jaundice since childhood. This patienthad been hospitalized two times in the medicine ward at 17 weeks and 33 weeks of gestation. Patient was diagnosed as crigler-Najjar syndrome type 2 at 33 weeks of gestation. Her total bilirubin level in pregnancy was in range of 10-20mg/dl. Her jaundice was persistent, though the severity fluctuated from time to time, increasing during periods of stress and pregnancy. Phenobarbitone treatment caused acute fall in bilirubin level. Pregnancy outcome was normal delivery of healthy newborn. Her newborn had mild indirect hyperbilirubinemia on day 3, did not require any treatment and his postnatal followup uptil 4 months showed normal growth and development.*
Conclusion: *Crigler-Najjar syndrome type 2 disease, a rare cause of maternal unconjugated hyperbilirubinemia in pregnancy, poses no threat to the mother, and the elevated bilirubin levels do not seem harmful to the fetus.*
Keywords: *Crigler Najjar type 2, Pregnancy, Phenobarbitone.*

Introduction

Crigler Najjar type 1 was first described in 1952 and its prevalence is 0.6 to 1 per million characterized by striking unconjugated hyperbilirubinemia with no detectable constitutive expression of UGT1A1 activity in hepatic tissue[3]. 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[4].

Crigler Najjar type 2 was recognized in 1962 as a distinct entity and characterized by marked unconjugated hyperbilirubinemia in absence of abnormalities of other conventional hepatic biochemical tests, hepatic histology and hemolysis. Crigler Najjar type 2 differs from Crigler Najjar type 1 in several ways like bilirubin concentration is low 6-25 (usually ≤20), infrequently associated with kernicterus, bile is deeply coloured and bilirubin glucronides are present with characterstic increase in proportion of monoglucronides, UGT1A1 (UDP glucuronosyltransferase 1-A1) in liver is usually present at reduced level(typically ≤10% of normal) and treatment with phenobarbitone decreases bilirubin by >25%. CN-2 is predominantly autosomal recessive condition[3]. There is no predilection to any race or sex. Crigler Najjar type 2 is a rare condition with an incidence of 1 per 1000000 births[5].

Patients usually present with jaundice in the first year of life but can sometimes present with jaundice in the third decade. Acute increase 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[6].

Case

The patient was a 25-year-old primigravida woman, admitted to our hospital with history of amenorrhoea for 9 months and jaundice since childhood. Her jaundice aggravated in pregnancy. There was no history of nausea, vomiting, headache, fever, pruritis, malena, hematemesis, blood transfusion or pain in the right hypochondrium.

Family history revealed that she has an unmarried brother who is also suffering from jaundice since birth and having unconjugated hyperbilirubinemia but has been not further investigated. The couple was non consanguineous. As per patient her parents had no history of jaundice. There was no history of congenital abnormalities, mental retardation, neonatal/infant death or neurological disorders in their families.

She was hospiitilized at 17 and again at 33 weeks of gestation. Diagnosis of crigler-Najjar syndrome type 2 was established at 33 weeks of gestation. At the time of 17 weeks gestation patient was admitted in view of fever since 3 days. Her haemoglobin was 8.3, platelet count was 1.5 lac, total bilirubin was 9.8 mg/dl and indirect bilirubin was 8.6 mg/dl. Her Liver enzymes were essentially normal (SGOT, SGPT, LDH) and there was no evidence of any coagulopathy. Her peripheral smear showed no evidence of hemolysis or malarial parasite. Her viral markers were negative, retic count was 0.6%, Indirect comb test was negative. Her ultrasound whole abdomen consisted of no significant findings. Her fever subsided within 2 days after taking some antipyretics. Patient was again admitted at 33 weeks of gestation with complaint of increase in yellowish discolouration of eyes, this time her total bilirubin was 19.4 mg/dl, indirect was 18.4 mg/dl, liver enzymes were normal, coagulation profile was normal, viral markers were negative and peripheral smear showed no evidence of hemolysis. Serum haptoglobin levels were also normal. The patient was started on oral phenobarbitone at a dose of 60 mg thrice daily. Concurrently, her blood sample was sent for genetic analysis. Patient was then followed up two weeks later. Post phenobarbitone therapy her total bilirubin levels fell rapidly by more than 50% to 10.2 mg/dl with an indirect fraction of 9.4 mg/dl. This typical fall in bilirubin levels was suggestive of CNS Type 2.Her TATA BOX SEQUENCING showed normal number of TA repeats, which is not suggestive of gilbert syndrome.

She was then admitted at 39 weeks 5 days gestation, her vitals were stable. Icterus was present. There was no pallor or cyanosis. Cardiovascular and respiratory systems were normal. On abdominal examination, liver and spleen were not palpable. The uterus was term size, with fetus in longitudinal lie with cephalic

presentation. The fetal heart rate was regular 136 bpm.

On vaginal examination, the cervical os was closed.

Investigations revealed Hb to be 13.1 g/dL, MCV 97.3 fl, MCH 36.7 and MCHC34.7 g/dl and platelet count of 1.5 lac/cumm. Total serum bilirubin was 11.1 mg/dl (unconjugated bilirubin 10.4 mg/dl and conjugated bilirubin0.7 mg/dl), SGOT - 38 IU/ L, SGPT - 25 IU/L, serum alkaline phosphatase - 214 IU/L and LDH -225 IU/L. Urine was negative for bile salts and bile pigments. Peripheral smear did not show any evidence of hemolysis. Coagulation profile was normal. Ultrasound scan revealed normal liver and spleen. All viral markers including hepatitis A, IgM and hepatitis E IgM were found to be negative.

Patient went in to spontaneous labor at 40 week 1 day gestation. She had a normal vaginal delivery of a female baby weighing 2.3 kg. The baby had a normal apgar score at birth. Post-partum period was uneventful.

She was managed conservatively and the serum bilirubin levels dropped gradually to 8.9 mg/dl with persistence of unconjugated hyperbilirubinemia. (unconjugated bilirubin – 8.4 mg%, conjugated bilirubin – 0.5 mg %).Rest investigations were in normal limits.

Examination of the newborn in the nursery was normal. Pallor was absent. No abnormalities were detected on the newborn's physical examination. The baby's weight was 2.3 kg and length 50 cm.

On day 3 of birth baby was icteric and investigations of the baby revealed serum bilirubin 6.2 mg% (unconjugated bilirubin - 5.6 mg%, conjugated bilirubin – 0.6 mg%), SGOT 48 IU/L, SGPT 54 IU/L and serum alkaline phosphatase 61 IU/L. Jaundice disappeared on day 8, without any treatment and was diagnosed as physiological jaundice. Baby was discharged, when her serum bilirubin level had dropped to 3.4 mg% (conjugated 0.2mg% and unconjugated 3.2 mg%). and there was no evidence of kernicterus.

Discussion

Crigler-Najjar syndrome (CNS) is a rare autosomal recessive disorder of bilirubin metabolism. Type I CNS is associated with severe jaundice and permanent neurologic damage (kernicterus). Type II CNS is associated with a lower serum bilirubin concentration and responds to phenobarbitone treatment.

Death is almost inevitable with CNS type I, only patients with type II and Gilbert syndrome are seen in the reproductive years. In view of the significant longstanding jaundice since childhood and isolated indirect hyperbilirubinemia, our patient was suspected to have a genetic disorder of bilirubin conjugation. A strong family history of persistent unconjugated hyperbilirubinemia, yellowish discolouration of eyes since childhood, normal coloured stools, absence of hemolysis and normal liver enzyme levels lead us to a diagnosis of Crigler Najjar Syndrome type II. Serum bilirubin levels in our case reached up to 19.4mg/dl, which ruled out Haemolytic syndromes and Gilbert's syndrome in which bilirubin levels rarely cross 6 mg/dl[7]. Hemolytic syndrome was further ruled out by normal peripheral smear and LDH level.

In Gilbert's, following phenobarbitone administration, the bilirubin levels completely normalise. In CNS type 2 the fall in bilirubin levels is usually more than 25 percent, but the levels never normalise. In CNS type 1, the fall is almost nil. The response in CNS type 2 with phenobarbitone is due to induction of the already present residual UGT1A1 (UDP glucuronosyl-transferase 1-A1) enzyme activity required for bilirubin conjugation[8].

There are several studies regarding placental bilirubin metabolism. Unconjugated bilirubin crosses the placental barrier to cause high levels of bilirubin in the fetus resulting in neurological damage (kernicterus) or even death[9].It seems reasonable to try to keep the maternal (and therefore the fetal) unconjugated bilirubin concentrations below 200 mmol/l (11.7mg/dl)and

the molar ratio between unconjugated bilirubin and serum albumin below 50%[10-11].

Treatment of CNS type 2 is usually conservative with avoidance of drugs that displace bilirubin from albumin like penicillin, sulphonamides, salicylates, ceftriaxone and furosemide[12].

The dose of phenobarbitone is 3-5 mg/kg/day titrated preferably to 60- 180 mg/ day in single or divided doses[13]. The dose is reduced further (30-60 mg/ day) in pregnancy to avoid its teratogenic side effects. The response is seen within two to three weeks. Adjuvant calcium supplementation has also been found to increase the gut excretion of bilirubin[14].

However, Crigler –Najjar disease type II seems to pose no maternal risk during pregnancy.

Furthermore, hyperbilirubinemia has no significant ill effect on the fetus in utero and baby's outcome is usually good with phenobarbitone, phototherapy and exchange transfusions[15]. Therefore, patients with type II disease can lead a normal reproductive life as it poses no threat to the mother or fetus.

In conclusion, we can propose that in pregnancy with crigler- Najjar disease type II, admission to hospital to facilitate monitoring and treatment of both mother and infant is necessary, maternal bilirubin serum levels should be kept below 200 mmol/l (11.7 mg/dl) , in CNS type 2 phenobarbital treatment seems to be a safe option. Neurologic follow-up including sensitive hearing tests of these children is recommended as hearing disorders are among the commonest sequelae of kernicterus[16].

This case has been reported because it is an extremely rare disorder. It emphasizes the existence of a rare differential diagnosis of jaundice in pregnancy and the significance of taking a detailed family history in a case of jaundice in pregnancy. In our patient a good outcome is noted in the mother and her newborn, which is a favourable message for other cases affected with this rare condition.

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Abbreviation

CNS - Crigler-Najjar syndrome
SGOT -Serum glutamic oxaloacetic transaminase
SGPT - Serum glutamic pyruvic transaminase
LDH - Lactate dehydrogenase
UGT1A1 - UDP glucuronosyltransferase 1-A1