Successful Pregnancy Outcome in Maternal Crigler Najjar Syndrome Type II.

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Citation

Abstract:
Estimated incidence of Crigler-Najjar syndrome(CNS) is 1 case per 1,000,000 births(1 million). The overall prevalence of CN syndrome is unknown, with only several hundred people reported to have this disease. It is interestingly very rare to encounter a pregnant adult women with congenital jaundice. Pregnancy in CN type II patients is a diagnostic and a therapeutic challenge because of the high risk of bilirubin encephalopathy with serious neurological damage as life-threatening complications for the fetus. To date 8 pregnancy outcome have been reported from 5 women and we report the 9th women with a successful 9th pregnancy outcome. We have discussed detail history, presentation and management during pregnancy and care of the new born.

Keywords: Crigler Najjar Syndrome type II; Unconjugated hyperbilirubinemia; Phenobarbitone; Phototherapy.

Introduction
Crigler Najjar Syndrome (CNS) is a rare autosomal recessive condition associated with two types in clinical practice. CNS Type I is characterised by complete deficiency and CNS type II by severely reduced activity of hepatic microsomal bilirubin-uridine 5-diphosphate-glucuronosyltransferase (UDPG-T)(1). First case of CNS type I was reported by Crigler and Najjar in 1952 which results in severe unconjugated hyperbilirubinemia and thus neurologic impairment (kernicterus) in the newborn. Affected individuals do not respond to Phenobarbitone therapy, need prolonged hours of intensive phototherapy, exchange transfusions and, without liver transplantation, usually die in infancy from kernicterus.(1,2) Arias first described CNS Type II, causes milder unconjugated hyperbilirubinemia and responds to phenobarbitral treatment and present with episodes of jaundice responding to phenobarbitone.(3-5) The gene coding for UDPG-T, UGT1A1, has been mapped to 2q37 and mutations associated with both type I and type II have been reported.(6-8) Maternal CNS type II is a rare clinical entity with only 8 pregnancies reported from 5 CNS type II pregnant women. We present the 9th pregnancy from 6th women with CNS type II. Due to paucity of information, we reviewed the literature and with the experience shared by authors,(9-17) were able to have a successful experience through out pregnancy, delivery and the puerperium and we are very grateful to all the authors.

Case Report:
A 27 year old Gravida 2, para 0, abortion 1, living 0, presented to us at 24 weeks of gestation, with complaints of malaise, low grade fever, yellow discolouration of sclera, high coloured urine. She revealed a past history of first episode of severe jaundice at 5 months of age requiring hospital admission, responded to phototherapy and daily dose of phenobarbitone. Multiple episodes of treatable jaundice were reported. As it is customary in hindu society(tamil origin), women being admitted repeatedly for problems are looked down upon and her mother took the help of ayurvedic practioner, which is indegenious to our country and had noticed alleviation of episodes of jaundice. Husband was also of tamil origin and was unaware of her situation. Following her first abortion 2 years back at 12 weeks of pregnancy associated with severe jaundice, she was investigated at a tertiary centre and produced a stamped referral slip as a case of Crigler Najjar syndrome type II. She responded to phenobarbitone 60 mg/day and 2 years later had a spontaneous conception, with no antenatal care at any medical centre. She looked deeply icteric and dehydrated with 24 weeks of pregnancy. After reviewing the earlier diagnosis and discussing with our gastroenterology colleagues we decided to treat her with tablet phenobarbitone 60 mg once a day, maintain hydration and supportive care. Her complete haemogram was normal, anti HIV , anti HbsAg , anti HBC, anti HBE antibodies were negative. She had raised total bilirubin of 13.3 mg/dl, conjugate bilirubin of 0.1 mg/dl, unconjugated bilirubin :13.2 mg/dl. Normal total proteins: 7.4 g/dl, albumin:4.1 mg/dl, normal liver enzymes.blood group was A negative and husband was A
positive Ultrasonography of upper abdomen was normal, without any organomegaly. Obstetric scan documented a single live intrauterine pregnancy with fetus in breech, corresponding to dates, normal placenta, liquor volume and no gross congenital anomaly. A fetal echo performed was normal. She was kept on follow up every 2 weekly and we plotted her unconjugated bilirubin levels as shown in figure-1. At 29 completed weeks she had an episode of premature contractions and so we administered steroids to enhance fetal lung maturity. Her unconjugated bilirubin levels were between 8-9 mg/dl.We continued with phenobarbitone, oral haematinics, calcium, multi vitamin and protein supplements. She went into spontaneous labour at 35-36 weeks of pregnancy and delivered a live male baby weighing 2200 grams, length of baby was 43 centimeters with an umbilical length of 34 cms and shifted neonatal intensive care unit. Neonate had the following Haemoglobin was - 16.9 gm%, PCV: 57.3%, reticulocyte count-0.3%, total WBC count - 10,000 cells/mm3, Platelet count: 1.95 lakh/ mm3 PBS: normocytic and normochromic Blood group and type A: positive. Direct Coombs Test was negative. Total bilirubin- 12.1 mg/dl, direct- 0.6, indirect- 11.5, C-Reactive Protein- 26 mg/litre. Neonatal hyperbilirubinemia table-2 and hypoglycaemia were treated with Intravenous Phenobarbitone. 5 mg/kg body weight 12 hrly and dextrose bolus respectively. By 16 hours of birth baby needed phototherapy as his total bilirubin was stalling. Hence, intensive phototherapy has to be started, total serum bilirubin levels started to decline, by day 5 total Serum bilirubin reached values below 5 mg/dl and declined to reach 3.3 mg/dl and 1.3 mg/dl by day 8 and 14 respectively. Baby was discharged on day 14.

Discussion
Crigger-Najjar Syndrome (CNS) is a rare autosomal recessive disorder of bilirubin conjugation as substantiated by many authors.(6-8) Incidence of CNS is probably less than 1 case per 1,000,000 births. Only a few cases have been described in literature and the exact prevalence is unknown (Table-1).

Type I presents at birth and is more severe form associated with kernicterus and neurologic morbidity, whereas, type II CNS has late neonatal presentation, lower serum unconjugated bilirubin concentration, which responds to phototherapy and phenobarbital therapy. Due to the rarity of the condition, about 4 pregnancies have been reported in 4 cases of maternal CNS type I and 8 pregnancies from 5 maternal CNS type II (Table-1).

With the knowledge we gained by reviewing the literature we realised it would be prudent to start phenobarbital therapy from her past history, rather than debate her genetic basis and perform a liver biopsy which we anyway declined. Gilbert’s syndrome was the other possibility, usually it presents with hyperbilirubinemia during puberty possibly because of the inhibition of bilirubin glucuronidation by endogenous steroid hormones. Anti HIV, anti HbsAg, anti HBC, anti HBE antibodies were negative ruling out hepatitis, she was not in sepsis as total count was 10,000 cells/mm3. Her blood group was A Rh typing was negative. We kept her on a close follow up for every two weekly serum total, conjugated and unconjugated bilirubin levels which is depicted in Figure-1.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Disease type</th>
<th>Maternal serum bilirubin, mg/dl</th>
<th>Maternal treatment</th>
<th>Delivery</th>
<th>Newborn treatment/ outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al (9), 1991</td>
<td>CNS type I</td>
<td>17–21.8</td>
<td>None</td>
<td>Caesarean section</td>
<td>Phototherapy/ quadriplicate</td>
</tr>
<tr>
<td>Smith et al(10), 1994</td>
<td>CNS type II</td>
<td>5.3–9.6</td>
<td>None</td>
<td>Spontaneous, vaginal, at term</td>
<td>No treatment required/normal</td>
</tr>
<tr>
<td>Ito et al(11), 2001</td>
<td>CNS type II (2 pregnancies)</td>
<td>NA</td>
<td>Phototherap y, Phenobarbit al</td>
<td>Primary caesarean section</td>
<td>NA, Normal</td>
</tr>
<tr>
<td>Holstein et al (12), 2005</td>
<td>CNS type II</td>
<td>4.2–8.9</td>
<td>Phototherap y, Phenobarbit al</td>
<td>Phototherapy, Alumin infusions</td>
<td>Caesarean section</td>
</tr>
<tr>
<td>Pinkey et al(13), 2005</td>
<td>CNS type II</td>
<td>10.8 (at delivery)</td>
<td>Phototherap y</td>
<td>Spontaneous, vaginal, at term</td>
<td>Blood transfusion, phototherapy, phenobarbital/n ormal</td>
</tr>
<tr>
<td>Gajdos et al(14), 2006</td>
<td>CNS type I</td>
<td>13.5–23.5</td>
<td>Phototherap y, Albumin infusions</td>
<td>Phototherapy/normal</td>
<td>Phototherapy/normal</td>
</tr>
<tr>
<td>Passuello et al(16) V et al 2009</td>
<td>CNS type II</td>
<td>4–6 mg/dl</td>
<td>Photobarbitone and insulin for GDM</td>
<td>Vaginal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hannam S et al(17), 2008</td>
<td>CNS type I</td>
<td>200–300 micro mol/L</td>
<td>Phototherap y</td>
<td>Emergencyc cesarean</td>
<td>Phototherapy and phenobarbitone, double exchange transfusion</td>
</tr>
<tr>
<td>Hannam S et al(17), 2008</td>
<td>CNS type II</td>
<td>399–510 micro mol/L</td>
<td>Phototherap y, Albumin</td>
<td>Vaginal</td>
<td>Phototherapy and phenobarbitone, double exchange transfusion</td>
</tr>
<tr>
<td>Holstein et al(15), 2010</td>
<td>CNS type II, 2 pregnancies</td>
<td>4.2 mg/dl and 5.5 mg/dl until delivery</td>
<td>Phototherap y, Phenobarbitone</td>
<td>Both pregnancies primary caesarean section</td>
<td>No treatment required/normal</td>
</tr>
<tr>
<td>Shakuntala et al 2012, Present case</td>
<td>CNS type II</td>
<td>8.9 mg/dl until delivery</td>
<td>Photobarbitone</td>
<td>Spontaneous vaginal</td>
<td>Phototherapy and phenobarbitone/normal</td>
</tr>
</tbody>
</table>

Values have ranged from 4.2-10.8 mg/dl, present case it was maintained between 8-9 mg/dl on Phenobarbital therapy 60 mg daily. Similar observations were shared by other authors.(10-13,15,16) Good maternal and fetal outcomes have been reported when, dual treatment consisting of phototherapy during embryogenesis and phenobarbital during the rest of the pregnancy.(15) Though we did not have an opportunity to use phototherapy during the embryogenesis as the patient registered with us at 24 weeks, our maternal and fetal outcomes concur with Ito et al and Holstein et al, Passuello V et al(11,12,15,16) Rest of the pregnancy and antenatal care was carried out as usual procedure with the fetal anomaly scan, cardiac scan, growth parameter, liquor volume, placental volume, placental maturity all were correlating with the period of gestation. She had an episode of preterm pain at 29

Table 1: Review of literature
weeks of gestation and betamethasone 12 milligrams was given intramuscularly 24 hours apart to enhance lung maturity, to prevent the further burden on immature liver. However, she continued pregnancy and delivered a male baby weighing 2200 grams, length of 43 centimeters at 35-36 weeks of gestation. Baby had initial cyanosis and on bagging and masking the APGAR score improved. But, due to the high risk associated with preterm birth and maternal CNS type II 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 16 hours of birth total bilirubin levels were 11.5 mg/dl and 11.2 mg/dl even with commencement of f intravenous phenobarbitone 5 mg/kg body weight.hence intensive phototherapy was started at 16 hours of birth. Baby recovered by 8 days and was discharged on request by the parents. Baby had normal developmental milestones until 1 year of follow up. Similar treatment modalities and neonatal outcomes have been reported by some authors.(10,13,15,16)

We report this case due to its rarity, may be the 6th case of maternal Crigler-Najjar Syndrome Type II who successfully delivered the 9th such baby. When suddenly encountered by such pregnant women with congenital jaundice we were faced with a clinical dilemma, as to are we offering the correct standard of care to optimise the maternal and fetal outcome? This clinical scenario also highlights the importance of basic history taking and consider this condition also in the differential diagnosis of hyperbilirubinemia in pregnancy, which typically has elevated unconjugated bilirubin levels, normal liver enzymes and proteins, may be with an affected member in the family.

Data suggest that pregnancy need not be contraindicated in Crigler-Najjar Syndrome Type II. But prompt recognition and interdisciplinary involvement of paediatrician, obstetrician, gastroenterologists, blood bank officer and laboratory technician in these high risk pregnancies can achieve optimum maternal and fetal outcome( prevent neurologic morbidity and sequela).

Acknowledgement:
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References