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Interesting Cases

Possible Delayed Activation of Uridine Diphosphate Glucuronosyl Transferase (UGT) Enzyme causing Severe Unconjugated Hyperbilirubinemia in a Newborn

Bhabesh Kant Chowdhry[1], Royal Singh[2], Arun Prasad[2], Chandra Mohan Kumar[2], Shweta Singh[3]

[1]Department of Neonatology, All India Institute of Medical Sciences, Patna, Bihar, India.
[2]Department of Paediatrics, All India Institute of Medical Sciences, Patna, Bihar, India.
[3]Department of Biochemistry, MDBAS Medical College, Deoria, Uttar Pradesh, India.

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Corresponding Author:
Chandra Mohan Kumar, Department of Paediatrics, All India Institute of Medical Sciences, Patna, Bihar India.
E-mail Id:
cmkumar@aiimspatna.org
Orcid Id:
https://orcid.org/0000-0003-1076-6360
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A B S T R A C T

Neonatal jaundice is a common medical condition in newborns. Some babies require phototherapy but very few babies develop bilirubin encephalopathy or require exchange transfusion. Most of them are due to haemolytic conditions and UGT enzyme deficiency syndromes. We present a case with serum bilirubin > 50 mg/dl at presentation who required four times exchange transfusions and then recovered completely without residual damage, whose investigations revealed no plausible explanation for such high unconjugated bilirubinemia and the clinical course underlining the transient nature of the disease thus suspected of delayed maturation of UGT enzyme activity in a term neonate. UGT enzyme activity may remain absent in the early few days leading to severe unconjugated bilirubinemia requiring multiple exchange transfusions, however, complete enzymatic activation may happen by day 10 and the baby may recover without any residual damage.

Keywords: Neonatal Jaundice, Encephalopathy, Phototherapy, Conjugation

Introduction

Neonatal jaundice is a common medical condition in newborns. It is mostly physiological, however, some babies require phototherapy and rarely a few require double volume exchange transfusion (DVET). Common aetiologies of neonatal jaundice (NNJ) requiring exchange transfusion are haematological causes like Rh/ABO incompatibility, uridine diphosphate glucuronosyltransferase (UGT) enzyme deficiency like Crigler-Najjar Syndrome type 1 and 2, and sometimes severe sepsis and minor blood group incompatibility. However, with the increasing availability of better antenatal care and diagnostic facilities, the frequency of severe cases of unconjugated hyperbilirubinemia leading to bilirubin encephalopathy have decreased over the years and the proportion of these most commonly suspected aetiological conditions too is decreasing. In a study done in Delhi in 2018,no cause could be identified in 42%of cases requiring phototherapy.[1]

Here we present a case of suspected delayed enzyme maturation of UGT enzyme activity in a term neonate who required four times exchange transfusions, three Double Volume Exchange Transfusion (DVET) and one

Single Volume Exchange Transfusion (SVET) between the 7th and 10th days of life even while undergoing double surface phototherapy and supplemental intravenous (IV) fluid relaxation without any plausible known cause for serum bilirubin rising beyond 50 mg/ dl.

Case Report

A full term baby boy, delivered at home, with unknown birth weight, was presented to the paediatric emergency room on day seven of life, with yellowish discolouration and shrill cry for one day. The weight at presentation was 2.1 kg. Antenatally, the mother had irregular antenatal check-up visits, received iron and folic acid, 2 doses of Td vaccine, and had no history of fever with rash, drug intake, or radiation exposure, in the first trimester. There was no ho prolonged rupture of membranes (PROM) or peripartum fever. The baby cried immediately after birth. He was asymptomatic and was feeding satisfactorily on breastmilk for 6 days of life. On the 6th day, parents noticed decreased feeding and yellowish discolouration of the body. The baby also developed fever the next morning (7th day of life) and was taken to a paediatrician. Investigation showed serum bilirubin level of 50.6 for which he was referred to our hospital. There was no h/o vomiting, loose stools, increased work of breathing, or discharge from the umbilicus.

Ophisthotonus and dystonia were present at the time of admission. As the baby had fever and refusal to take feeds, sample for sepsis screen (CBC, CRP, Micro ESR) and blood cultures were sent along with Blood Grouping, Rh Typing, DCT, LFT, and KFT to rule out haematological/ haemolytic causes of hyperbilirubinemia as well as to assess for any organ dysfunction (MODS). A sample to rule out G6PD deficiency was also sent. Prophylactic antibiotics were given for suspected sepsis as per our NICU protocol. TSB level was 50.6 mg/dl, out of which, indirect bilirubin was 49.2 mg/ dl signifying very high unconjugated hyperbilirubinemia. To reduce the serum bilirubin levels, double surface phototherapy was started immediately, and simultaneously grouped and cross-matched blood was arranged for double volume exchange transfusion, and sample was sent for total serum bilirubin at the start of exchange transfusion. Pre-exchange IV fluid was started. Formula feeds of 10 ml were given through Oro-gastric (OG) tube every 2 hours on the first day and were then gradually increased to 30 ml/2 hr as OG feeds were well tolerated by the baby. The baby's blood group was B positive and DCT report came negative. Other investigation reports are given in Table 1. After the first DVET, bilirubin levels dipped but the level started rising again within hours and was still in the exchange zone, so repeat DVET was done. Then one SVET (due to unavailability of grouped and cross-matched blood) was done followed by another DVET in view of rising bilirubin levels even after exchange transfusions. Liver function tests and kidney function tests including serum albumin were in the normal range. In view of suspected enzyme deficiency as a cause of unconjugated hyperbilirubinemia (Crigler Najjar type 1 or 2), phenobarbitone was also given. The condition of the child significantly improved. Phototherapy was continued for 6 days and was stopped when bilirubin came below the phototherapy level. IV fluids were also stopped along with phototherapy. The baby was kept under close monitoring for any rebound hyperbilirubinemia. Table 1 contains the details of SB and interventions along with the timeline. Trial for Katori-spoon feed was started followed by breastfeeding which was tolerated by the baby. In the report of initial blood culture sent on the day of admission, Coagulase Negative Staphylococci (CONS) came positive but as the baby was clinically well from day 2 of admission and other septic screen came negative, IV antibiotics were stopped after a week and a repeat blood culture was sent which came negative. In view of very high unconjugated bilirubinemia in the absence of any haemolysis or other plausible explanation, UGT deficiency was suspected. The UGT1A1 enzyme being the key liver enzyme associated with bilirubin conjugation and metabolism, genetic analysis and assessment of enzyme activity were considered for diagnostic evaluation, considering Crigler-Najjar type1 as the most likely aetiology, but could not be done due to financial constraints. However, afterwards, the baby started improving, thus practically ruling out CNS-1 as that situation would have never improved without an orthotopic liver transplant. Phenobarbitone was stopped as the condition of the baby improved significantly. Repeat serum bilirubin was normal after one week of stopping phenobarbitone. Ophthalmologic evaluations were within normal limits. Hearing screening was done, OAE passed but BERA results were in the 'referral' category in both ears, and on follow-up visit repeated after one month, the reposts were normal. MRI brain was contemplated to assess for kernicterus but could not be done due to financial reasons. USG cranium was done instead which showed that both cerebral hemispheres were normal. Basal ganglia showed no abnormal echogenicity on USG. At follow up after one week of discharge, the baby was haemodynamically stable, neurological examination was normal, and serum bilirubin was 0.8 mg/dl confirming the transient nature of the condition.

The findings were similar in the one-month follow-up visit, thus reassuring complete recovery without any residual neurological sequelae.

Discussion

Although neonatal hyperbilirubinemia is one of the commonest metabolic disorders, most of them have no clinical complication and with improvement in antenatal diagnostics and postnatal care, DVETs are rarely required

nowadays.[2] Due to increased awareness and availability of anti-D, Rh incompatibility has become a rare cause of haemolytic disease requiring exchange transfusion.[3] Off late various studies have shown that congenital haemolytic anaemia is responsible for a lesser number of neonatal hyperbilirubinemia requiring phototherapy. In studies from California and Chandigarh[4,5] in the late 20th century, in 45-58% of cases, the cause was not known which is approximately identical to the Delhi study.[1] In our case, the baby blood group was B positive with DCT negative and the mother was O positive with ICT negative, so Rh incompatibility or minor blood group incompatibilities were excluded. Other possible aetiologies which may present with elevated serum bilirubin in exchange transfusion range like G6PD, RBC membrane defect were excluded as G6PD and peripheral smear were normal and also haemoglobin was 17 gm/dl at the time of admission when serum bilirubin was above 50 mg/dl. Causes of TORCH infection, sepsis, and hypothyroidism were also excluded by investigation. Even though the coagulase-negative staphylococci were isolated from blood culture, clinically the child remained well after the 2nd day of admission and sepsis screen was negative. After ruling out almost all commonly diagnosed aetiologies associated with very high unconjugated hyperbilirubinemia, initially Crigler-Najjar type 1 was suspected. Because UGT1A1 is the sole bilirubin conjugating enzyme[6], enzyme defect was suspected in view of the baby requiring four exchange transfusions but due to financial constraints, UGT enzyme activity levels and UGT1A1 genetic analysis could not be done as it would have led to an expenditure of around 250 USD. Table 2 summarises the differential diagnoses and points in favour of and against them. After the 10th day of admission and four exchange transfusion, serum bilirubin started falling, on the 11th day, it became normal (6.4 mg/dl), and by the 15th day of admission, it came down to 1.8 mg/dl. Seeing this trend of serum bilirubin level and excluding other known causes of unconjugated hyperbilirubinemia, we came to a conclusion of a possibility of delayed maturation or activation of conjugated hepatic/intestinal UGT enzyme system. Conjugation of bilirubin is necessary to become water-soluble and excretion from the body for which enzyme activity is required.

Table 1.Investigations at Initial Assessment and Serum Bilirubin Levels with Timeline and Interventions

Admission Investigations	Mother Blood Group - O positive, ICT negative TORCH - IgM positive: toxoplasma, Rubella, CMV & HSV2	Baby	Blood Group - B positive, DCT negative TORCH - IgG positive for Rubella and HSV1	CBC - Hb 17.1 gm/dl, Reticulocyte Count 1.84%, Total Platelet Count - 4.5 lakh/micro litre (mcL), WBC - 12900 mcL PS - No feature suggestive of haemolysis	CRP-Negative < 2.8mg/L	Biochemical - Serum Bilirubin: Total - 50.6 Direct - 1.4 Indirect - 49.2 KFT - Na 134 mEq/L, K 5.5 mEq/L, Bl urea 28.5 mg/dL, S creatinine 0.35 mg/dL TFT - TSH 3.42 mIU/L, T4 18.59pmol/L G6PD - Normal
Serum Bilirubinmg/dl (hours)		2 hr	4 hr	6 hr	12 hr	INTERVENTION
Postnatal age	Pre-transfusion: Total - 50.6	Total SB: 31.8 Direct - 1.4	Total SB - 34.33 Direct - 2.8			Phototherapy (DSPT) continued Double Volume Exchange Transfusion (DVET) was done at bilirubin 50.6 mg/dl.

7th	Direct - 1.4 Indirect - 49.2					Persistence of SB above exchange level after 4 hours prompted another DVET which was done 10 hours after the first DVET.
8th		Total SB: 28.8 Direct - 1.1	Total SB: 30.1 Direct - 1.7			Phototherapy (DSPT) continued Single Volume Exchange Transfusion was done 12 hours after the second DVET
9th		Total SB: 28.1 Direct - 1.5	Total SB: 32.6 Direct - 1.9	Total SB: 28 Direct - 1.47		Phototherapy (DSPT) continued Double volume exchange transfusion was done 12 hours after the third DVET
10th	Immediate post transfusion: Total SB: 17.23 Direct - 0.59	Total SB: 21.45 Direct - 1.04	Total SB: 25.25 Direct - 1.19		Total SB: 17.43 Direct - 1.63	Phototherapy (DSPT) continued
11th	Total SB: 16.3 Direct - 0.94				Total SB: 6.43 Direct - 1.18	Phototherapy discontinued
12th	Total SB: 4.4 Direct - 0.82					
13th	Total SB: 3.48 Direct - 0.87					
15th	Total SB: 1.84 Direct - 0.4					

Table 2.Differential Diagnoses considered with Points in Favour and Against

S. No.	Differential Diagnosis of Hyperbilirubinemia	Point (s) in Favour	Point (s) Against
1.	Rh incompatibility	Presenting with increasing unconjugated hyperbilirubinemia	Both baby and mother were Rh positive
2.	ABO incompatibility	Presenting with very rapidly increasing unconjugated hyperbilirubinemia and mother being O positive, baby being B positive	DCT and ICT were negative.Also, haemoglobin of the baby at admission was 17 gm/dl and no haemoloysis feature was found in peripheral smear.

3.	Neonatal sepsis	First blood culture came to be CONS positive	CBC, CRP were normal, baby was clinically well (no other feature of sepsis except hyperbilirubinemia) and also unconjugated hyperbilirubinemia
4.	Hypothyroidism	Presenting with unconjugated hyperbilirubinemia	TSH 3.4, Tone and activity normal
5.	TORCH infection	Although mother was IgM positive for Toxoplasma, Rubella, CMV and Herpes simplex virus 2	Baby was IgG positive for Rubella and Herpes 1. The baby was only IgG positive which means chances of active disease were very less likely.
6.	Crigler-Najar syndrome	Our initial diagnosis was Crigler-Najar syndrome (CNS-1) type 1 as bilirubin was 50 mg/dl which was very high found almost exclusively with CNS-1.	Later bilirubin came to be within normal limit and did not rise again even after stopping phototherapy and in follow-up also, bilirubin remained normal without any treatment.
7.	Pyruvate kinase deficiency	Presenting with unconjugated hyperbilirubinemia	No feature of haemolysis in peripheral smear and Hb was 17 gm/dl in spite of serum bilirubin being 50 mg/dl at the time of admission.
8.	G6PD deficiency	Male baby presenting with unconjugated hyperbilirubinemia	G6PD level done and was normal and no feature of haemolysis in peripheral smear, Hb was 17 gm/dl in spite of serum bilirubin 50 mg/dl at the time of admission.
9.	Breast milk jaundice	Presenting with hyperbilirubinemia, clinically fine	Baby came to our hospital on day 6 of life. Breast milk jaundice generally peaks after 3 weeks and recedes much slowly.
10.	Breastfeeding jaundice	Presenting with unconjugated hyperbilirubinemia	Breastfeeding jaundice usually occurs in the early first weeks of life due to poor breastfeeding. This baby was feeding well till 6 days and also serum sodium was 134 meq/l which is normal while in breastfeeding jaundice signs of severe dehydration, poor feeding, and high serum sodium levels are hallmarks.
11.	Delayed maturation of UGT enzyme	Presenting with unconjugated hyperbilirubinemia Non-haemolytic Delayed but spontaneous resolution started after day 10 of life	Genetic testing for UGT1A1 mutations and enzyme UGT activity level not done due to financial constraints

Maturation of conjugation appears to favour the formation of monoconjugates initially. This conjugation makes toxic bilirubin water-soluble and non-toxic.[7] Ono H et al. showed in their study that delayed maturation of the liver could be one of the causes of transient galactosemia in the first 2 months after birth.[8] Here we postulate that delayed maturation of UGT enzyme may lead to unconjugated hyperbilirubinemia as severe as CNS-1.

Hundreds of mutations in the uridine diphosphate glucuronosyl transferase gene (UGT1A1 gene) are described in the literature but all those described mutations lead to either the absence or the reduction of UGT enzymatic activity.[9] No such case of delayed expression of enzymatic activity is reported in literature and that makes our case unique. The deficiency of enzyme activity in the first 10 days was so complete that it behaved like Crigler-Najjar type1 in which the SB crossed 50 mg/dl and required 4 exchange transfusions in 4 days but afterwards, serum bilirubin fell down to completely normal range and it remained so in repeat tests as well as in follow-up visit suggesting complete activation of enzymatic activity. Although it has been demonstrated that at birth, the UGT enzyme activity is just 1% of the normal adult levels, irrespective of gestational age, it increases to adult levels by the 14th week of life,[9] and hepatic enzyme activity on days 8-28 are identical in preterm as well as term babies irrespective of gestational age,[10] no such case is reported where an enzyme level recovered to normal from being absent and serum bilirubin wentabove 50 mg/dl which has been seen exclusively with Crigler-Najjar Syndrome-1.

What is known?
Neonatal unconjugated hyperbilirubinemia is a common condition in newborns but very few babies develop bilirubin encephalopathy or require exchange transfusion. Most of them are due to haemolytic conditions and UGT enzyme deficiency syndromes.
What does this case add?
UGT enzyme activity may remain absent in the early few days leading to severe unconjugated bilirub in emiarequiring multiple exchange transfusions. However, complete enzymatic activation may happen by day 10 and the baby may recover without any residual damage.

Conclusion

There is at present no case report of hyperbilirubinemia presenting with bilirubin encephalopathy and requiring multiple exchange transfusions due to delayed enzyme maturation. Even though without genetic testing this can only be hypothesised, and not concluded, this case report alerts clinicians about such a possibility and further genetic studies are needed to recognise the mutation which can have delayed expression of the UGT enzyme.

Authors' Contributions

Dr Bhabesh Kant Chowdhry conceptualised and prepared the manuscript draft. Dr Royal Singh and Dr Arun Prasad helped in case management and data collection. Dr Shweta Singh helped in the review of literature and drafting the manuscript. Dr CM Kumar reviewed the manuscript and did critical revision and gave final approval.

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Compliance with Ethical Standards

Ethics: Being a case report, IEC Approval was not needed. However, for the publication of this case report, verbal informed consent was taken from the parent.

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Conflict of Interest: None

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