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CLINICAL MEET

A RARE CASE OF PROLONGED JAUNDICE IN AN INFANT

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THE STORY

A 32days old male infant, born to a healthy mother, was brought to the hospital with complaints of yellowish discoloration of eyes and skin since 10 days

HISTORY OF PRESENTING ILLNESS-

- Apparently asymptomatic 10 days ago

- Complaints of yellowish discoloration of eyes followed by yellowish discoloration of skin

- The icterus was gradual in onset, exhibiting cranio-caudal progression, first noticed as yellowish discoloration of the eyes, which progressed to involve palms and soles

- Complaints of recurrent episodes of vomiting since 2-3 days, post feeding - non projectile, containing milk, non bilious, non blood stained associated with abdominal distension

HISTORY OF PRESENTING ILLNESS-

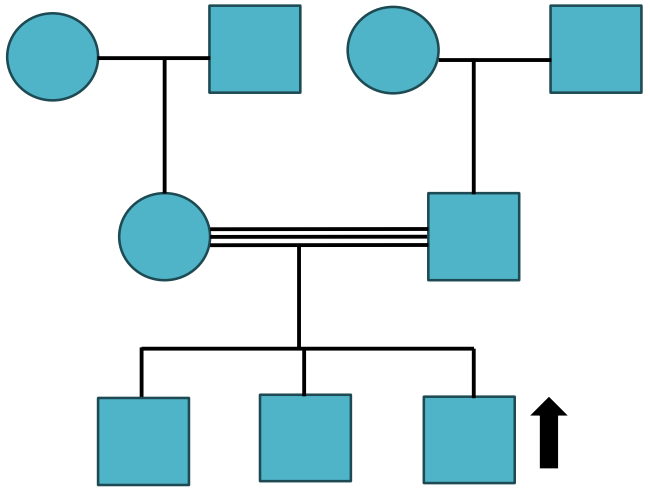
- Icterus was not associated with rash, bruising or bleeding from any orifices
- No episodes of loose stools, clay colored or foul smelling stools, no complaints of dark colored urine
- No episdoes of fever, seizures, decreased urine output
- ABO and Rh blood group incompatibility was not noted between mother and the baby

- **Antenatal history of the mother-**
- Not significant, no history of fever with rash

- **Birth history-** Uneventful
- Full term baby
- Mode of delivery- Caesarean section in view of previous Caesarean section
- Birth weight of 2.7 kg
- No resuscitation needed

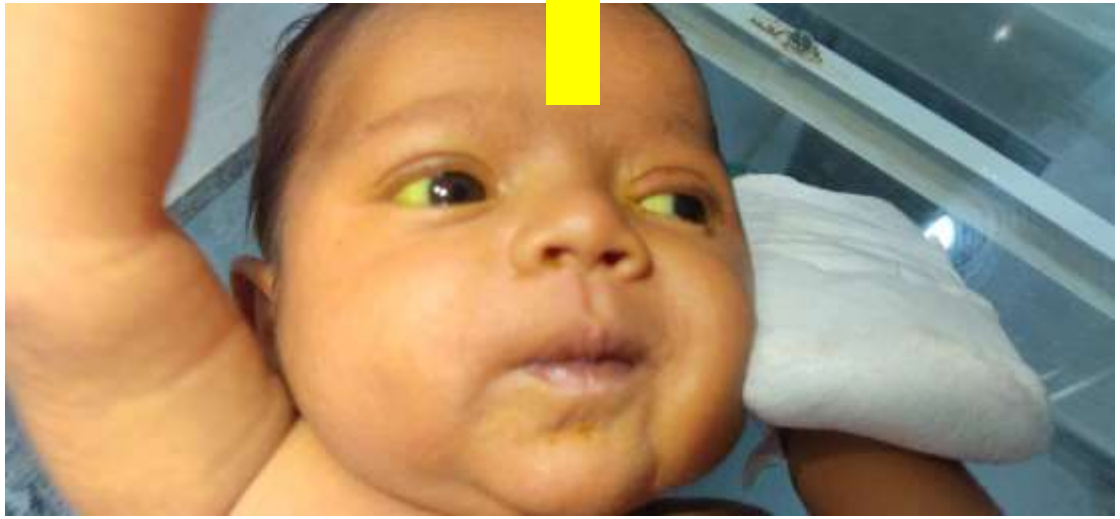
- **Post natal history-**
- Well fed baby on breastfeeds, showing good weight gain

- **Family history-** Third degree consanguineous marriage between parents
- No significant family history, no apparent history of jaundice during parents' childhood.
- No history of similar complaints in the elder siblings.



- **Development history-**
- Can sustain eye contact for few seconds, smiles
- **Immunisation history-** Immunised with birth dose
- **Diet history-** Exclusively breastfed baby

We are dealing with prolonged jaundice primarily



General Examination,

- Irritable but getting consoled by the mother
- Icterus present- involving skin over entire body from head to heels
- No evidence of petechiae, edema or any bleeding manifestations
- No dysmorphic features or peculiar body odour
- Anterior fontanelle open, full, non bulging, & posterior fontanelle closed

Anthropometry-

PARAMETER	VALUE	CENTILE
LENGTH	54cm	25^{TH} TO 50^{TH}
WEIGHT	3.490kg	3^{RD} TO 10^{TH}
HEAD CIRCUMFERENCE	36.5cm	25^{TH} TO 50^{TH}
ABDOMINAL GIRTH	35cm	

Vitals-

Temperature- 98.3F

Heart rate- 124/min

Respiratory rate- 46/min

Spo2- 100% on room air

Peripheral pulses- well felt

Capillary refill time- less than 2 seconds

BSL- 112mg/dL

Systemic examination-

CNS- irritable
Cry, tone, reflexes- appropriate for age

CVS- heart sounds normal, no murmur

RS- Air entry bilaterally equal, no added sounds

Per abdomen- soft, non tender,
mild distension present
No hepatosplenomegaly present

BIND SCORE – (Bilirubin Induced Neurologic Dysfunction)- for severity of jaundice

SEVERITY	MENTAL STATUS	MUSCLE TONE	CRY	SCORE
NORMAL/0	NORMAL	NORMAL	NORMAL	-
MILD/1	SLEEPY POOR FEEDING	NECK STIFFNESS, VARIABLE HYPOTONIA	HIGH PITCHED	-
MODERATE/2	LETHARGIC IRRITABLE	ARCHING NECK ARCHING BACK	SHRILL	2
SEVERE/3	SEMICOMA SEIZURES COMA	BOWING TRUNK OPISTHONOUS	INCONSOLABLE	-

SCORES-

Less than 3- stable

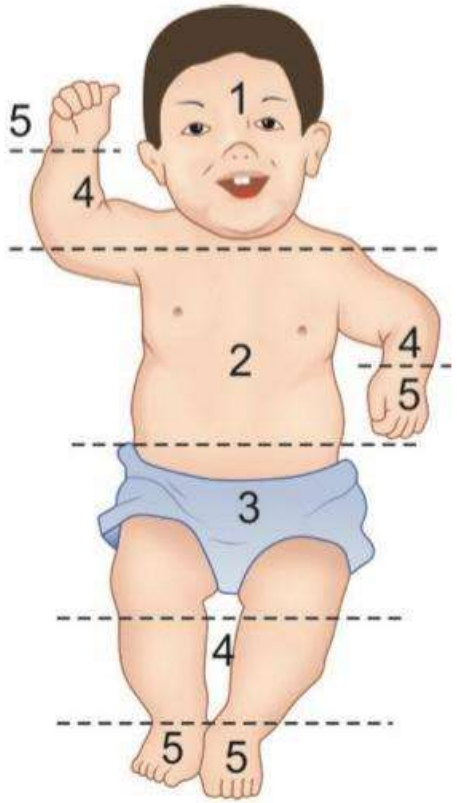
3-6: moderate risk

More than 6- Severe risk

ON ADMISSION BIND SCORE- 2

KRAMER SCORING – FOR CLINICAL ESTIMATION OF BILIRUBIN LEVELS

Visual Assessment by Kramer Criteria		
1.	Face	4–8 mg/dL
2.	Upper trunk	5–12 mg/dL
3.	Lower trunk and thighs	8–16 mg/dL
4.	Arms and lower legs	11–18 mg/dL
5.	Palms and soles	>15 mg/dL



TOTAL SCORE - 5

Based on the clinical history, examination & assessment following **differential diagnoses** were considered-

- Prolonged breast milk jaundice
- Hypothyroidism
- Late onset neonatal sepsis
- Neonatal cholestasis
- G-6-PD deficiency
- Rare cause of hemolysis- Hemolytic disease of newborn secondary to Minor blood group incompatibility
- Non hemolytic causes of jaundice-

1) Gilbert syndrome
2) Crigler Najjar syndrome type 1 or 2

On Day 1 of admission–

CBC, LFT sent-

- Hemoglobin – 10.4 g/dL (Anemia)

- Serum bilirubin- 33.3 mg/dL
- Direct bilirubin- 0.64 mg/dL
- Indirect bilirubin – 32.7 mg/dL (Predominant indirect hyperbilirubinemia)

The baby was suspected to have pathological jaundice initially and was started on intensive double surface phototherapy in ward.

Exchange transfusion was not considered in view of low BIND score on admission.

During the course of hospital stay,

- Serial hemogram and serum bilirubin levels were sent - hyperbilirubinemia along hemolysis was monitored
- Response to phototherapy was gauged
- Predominantly, indirect hyperbilirubinemia persistent
- Mild hemolysis noted- gradual fall in hemoglobin levels
- Upon stopping phototherapy, rise in serum bilirubin concentration was noted

LABORATORY INVESTIGATIONS

	02/02 DAY 1	03/02	05/02	07/02	08/02	09/02	10/02	11/02	12/02
HB	10.4		9.6	8.6	8.8	8.5	8.9	8.4	8.8
HCT	29.3		27	24.5	25.2	24.3	25.2	23.7	25.6
T. BILI	33.37	27.25	18.58	13.3	13.84	16.09	18.58	15.44	12.10
C. BILI	0.64	0.53	0.49	0.44	0.40	0.41	0.45	0.41	0.37
UC. BILI	32.73	26.72	18.09	12.89	13.44	15.68	18.13	15.03	11.73

FOR CAUSE OF HEMOLYSIS :

- Retic count 1.2
- DCT and ICT of mother and baby- negative
- ICT of mother- negative

Peripheral Blood Smear - normocytic normochromic cells with anisopoikilocytosis. Few polychromatic cells, target cells, occasional macrocytes, few spherocytes and occasional nucleated RBCs seen. Smear showed evidence of hemolysis.

Minor blood group incompatibility was suspected and was confirmed with diagnostic blood tests-
Rh extended blood group of baby- C C e e K
Rh extended blood group of baby- C c e e K

- TFT - within normal range, which ruled out hypothyroidism

- Sepsis screen including urine routine and microscopy, CRP and blood and urine culture & sensitivity- negative

  Thus, ruling out late onset neonatal sepsis

- Breast milk jaundice was ruled out by transiently withholding breastfeeds for 24 hours- after which drop in bilirubin could not be noted

- TORCH titres- negative
- G-6-PD – normal

- USG abdomen + pelvis – normal and absence of direct hyperbilirubinemia ruled out neonatal cholestasis

- Such high levels of indirect bilirubin ruled out hemolytic disorders and raised suspicion towards hereditary causes- such as Crigler Najjar and Gilbert syndrome

- Although the evidence of hemolysis was misleading at first,

association of minor blood incompatibility with hereditary cause of unconjugated hyperbilirubinemia was considered.

- Hence, enzyme mutation studies were sent.

Specific analysis for UGT1A1 mutation by sequencing showed low activity of the enzyme-

Patient carries homozygous UGT1A1 *28 allele

ENZYME MUTATION (UGT1A1) ANALYSIS BY SEQUENCING

Mutation	PATHOGENIC MUTATION DETECTED (HOMOZYGOUS)

Alleles	Effect of Patient's Polymorphism	Number of alleles detected
UGT1A1* 1 A(TA)6TAA	Normal enzyme activity	0
UGT1A1* 28 A(TA)7TAA	**Low enzyme activity**	2

***UGT1A1* Exon Mutation Analysis:**	
Mutation	**Genotype Detected**
p.G71R	Normal
p.Y486D	Normal

- Taking into account the clinical profile, initial indirect bilirubin values and enzyme mutation report, the child was diagnosed to fall under Crigler-Najjar syndrome type 2.

- However, Gilbert syndrome could not be ruled out entirely (as both syndromes have low enzyme activity)

- Lack of whole exome sequencing being a limitation in this case (unaffordability issues)

- The baby was started on oral phenobarbitone therapy, which led to a gradual decrease in serum bilirubin concentrations which reinforced our diagnosis.

- Discharged on continued phenobarbitone therapy in the same dose and advised for home phototherapy, with a phototherapy unit arranged for them for home

- Genetic counselling was done for parents and long term therapy was advised

- On first follow up, 1 week after discharge- serum bilirubin levels showed a significant decrease

- The patient has been following up twice weekly and so far showing improvement with the treatment advised

Follow up advice –

- A weekly follow up to closely monitor response to therapy was advised for 6 months.
- Regular ophthalmic evaluation
- Brainstem evoked audiometry- for sensorineural hearing loss
- MRI Brain at 3 months of age
- Developmental OPD enrollment and regular follow up

Thus, we have a case of prolonged indirect hyperbilirubinemia due to Crigler Najjar Syndrome-type 2 with associated minor blood group incompatibility

In order to understand our diagnosis better-

Discussion on Disorders of Bilirubin Metabolism-

Indirect hyperbilirubinemia-

- Crigler- Najjar syndrome (type 1 and 2)- (bilirubin- uridine diphosphoglucuronate glucuronosyltransferase mutations)

- Gilbert disease

Direct hyperbilirubinemia-

- Dubin Johnson syndrome (multiple drug resistant protein 2 mutation)

- Rotor syndrome

CRIGLER-NAJJAR SYNDROME TYPE 2

- Autosomal recessive inheritance, prevalence 0.6 to 1 in a million newborns worldwide for both type 1&2 (exact prevalence of CJ type 2 is not known)
- PARTIAL GLUCURONYL TRANSFERASE DEFICIENCY
- Caused by homozygous point mutation in UGT1A1 resulting in reduced (partial) enzymatic activity
- Usually manifests during neonatal period
- Serum bilirubin concentration can be in range of physiological or pathological jaundice- can remain elevated beyond 3rd week of life- persisting between 1.5-22 mg/dL

CRIGLER-NAJJAR SYNDROME TYPE 2

- Kernicterus is unusual, stools are of normal color.
- Whereas in type 1 disease, serum bilirubin reaches 25-35 mg/dL without treatment within first month of life, this can cause kernicterus. Stools are pale yellow.

- No evidence of hemolysis is present in Crigler Najjar type 1 and type 2
- Direct hyperbilirubinemia to some extent- present in type 2
- Liver enzymes, serum albumin and PT INR are within normal range
- Histopathological studies reveal microscopically, bile plugs occasionally within canaliculi as a result of cholestasis. There may or may not be hepatic parenchymal injury

CRIGLER-NAJJAR SYNDROME TYPE 2

- Genetic analysis to detect the types of mutation in the gene encoding UGT1A1 enzyme. Prenatal diagnosis - genetic analysis of chorionic villus sampling or amniotic fluid aspiration

- Treatment is phenobarbitone therapy in CJ type 2
- Response is seen as decrease in serum bilirubin to 2-3 mg/dL within 7-10 days of starting phenobarbitone therapy

- Mechanism- promotor for UGT1A1 activity in liver

- A marked reduction in serum bilirubin level occurs in CJ type 2 after treatment with phenobarbitone. This is a differentiation feature between type 1 and 2

CRIGLER-NAJJAR SYNDROME TYPE 2

- Plasmapheresis- most effective process to remove the excess unconjugated bilirubin in severe hyperbilirubinemia crisis

- Gene therapy: Introduction of a normal UGT1A1 gene can potentially cure the genetic defect - ex vivo gene and vector-mediated gene delivery (most effective vector- Adenovirus)
- Plans for clinical trials in humans are presently underway

- Hepatocyte transplantation- used a bridge therapy

- DEFINITIVE TREATMENT-

- In patients who develop fibrosis, liver transplant is being considered as a curative option
- A European retrospective study (2021) showed 86-100% survival rate at 1 year, 81-95% at 5 years and 79-92% at 10 years

CRIGLER-NAJJAR SYNDROME TYPE 2

PROGNOSIS AND OUTCOME-

- Crigler Najjar type 1 syndrome has a poor prognosis - may require emergent treatment during the hyperbilirubinemia crisis
- Kernicterus may be irreversible

- Due to some activity of the UGT enzyme, Crigler-Najjar type 2 syndrome may be asymptomatic or have mild symptoms, has a better prognosis than type I

To favour the diagnosis,

	GILBERT SYNDROME	CRIGLER-NAJJAR SYNDROME TYPE 1	CRIGLER-NAJJAR SYNDROME TYPE 2
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Onset	Prepubertal period	Early neonatal period	Late neonatal period
Pathology		UGT1A1 DEFICIENCY	PARTIAL UGT1A1 DEFICIENCY
Serum bilirubin levels	Upto 5mg/dL	30-40mg/dL	18-30mg/dL
Kernictrus	Absent	Present	Absent
Course of jaundice	Benign	Persistent severe jaundice	Persistent jaundice exacerbated by acute illnesses
LFT	Normal range	Normal range	Normal range
Response to phenobarbitone	Excellent (completely normal bilirubin levels)	Nil	Mild to moderate (bilirubin levels don't normalise)
Treatment	Not required usually	Liver transplant	Phenobarbitone + Liver Tx
Liver biopsy	Lipofuscin pigment	Normal	Normal

TAKE HOME MESSAGE-

- Severe hyperbilirubinemia has the potential to cause irreversible brain damage. Hence, prompt diagnosis and treatment is of utmost importance
- In cases of prolonged jaundice, think first – neonatal cholestasis
- Secondly, rule out prolonged breastfeeding jaundice, hemolysis, hypothyroidism, sepsis and G-6-PD deficiency
- For such unusual presentations, think of non hemolytic causes of indirect bilirubinemia
- Crigler Najjar Syndrome Type 2 is a rare genetic disorder of bilirubin metabolism
- A high level of clinical suspicion based on some of its unique features can avoid many extraneous and costly investigations. Hence, a patient presenting with asymptomatic indirect hyperbilirubinemia should be evaluated for Crigler Najjar Syndrome

MULTIDISCIPLINARY APPROACH-

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THANK YOU