ผู้ป่วยทารกชายไทย อายุ 4 เดือน

ภูมิลำเนา จ.สงขลา

- **CC : ส่งตัวมาจากรพ.จังหวัดด้วยเรื่องตัวเหลือง**
- **PI:** 3 เดือนก่อนมารพ. มารดาเริ่มสังเกตเห็นว่าผู้ป่วยมีอาการตัวเหลืองตาเหลือง ไม่ซึม ดูดนมปกติ ถ่ายอุจจาระและปัสสาวะสีเหลืองปกติดี

  2 เดือนก่อนมารพ. มารดาสังเกตเห็นว่าผู้ป่วยมีอาการตัวเหลืองตาเหลืองมากขึ้น แต่อาการอย่างอื่นปกติ จึงพาไปตรวจรักษาที่โรงพยาบาลจังหวัด

Present illness (cont.)

Investigation (รพ. สงขลา) :

- MB 29.7, DB 0.48 mg%
- มารดาและผู้ป่วย Blood group B Rh positive
- Reticulocyte count 2.7 %
- G6PD level, LFT, TFT: normal
- USG upper abdomen : normal

Present illness (cont.)

Treatment:

-Total blood exchange transfusion x 1 time

→MB 14.5 mg% , Hospital course ~ 2 wks.

-F/U OPD : MB 23-25 mg%

→Refer to KCMH

- **Perinatal History**
- G2A1P1 คลอด normal delivery, BW 3,144 gm หลังคลอดแข็งแรงดีกลับบ้านพร้อมมารดา

- **Past history :**
- Immunization : BCG1, OPV2, DTP2, HBV3
- Growth and development : คว่ำหงายและคว้าของได้ ส่งเสียงอ้อแอ้

Family History

- ปัจจุบันมารดาอายุ 30 ปี บิดาอายุ 31 ปี แข็งแรงดี
- มารดาเคยแท้งบุตรหนึ่งครั้งตอนอายุประมาณ 18 ปี
- ปฏิเสธโรคในครอบครัว
- ปฏิเสธประวัติการแต่งงานในเครือญาติ

Physical examination

- **V/S**: T 37^0C, HR 90 , RR 32/min,BP 90/60 mmHg
- BW 7.3 kg (P75) Height 63.5 cm (P50)HC43 cm (P50)
- **GA :** Thai male infant, alert, not pale, marked jaundice
  no dysmorphic feature
- **Skin:** Yellowish skin
- **HEENT** : AF 0.5*0.5 cm, PF closed, marked icteric sclera, not pale conjunctiva, cervical lymph node not enlarged.
- **RS** : normal breath sound, no adventitious sounds
- **CVS** : normal S1S2, no murmur

Physical examination (cont.)

- **Abdomen** : soft, not distended, active bowel sound, liver just palpable (span 5 cm), spleen can't be palpated, no ascites
- **Extremities** : no rash, no edema
- **NS:** Normal muscle tone, active and symmetrical movement, DTR 2+ all, BBK-Dorsiflexion both, no sustained clonus, motor grade V/V

Problem lists

"Prolonged unconjugated hyperbilirubinemia"

Investigation

- **CBC :** Hct 33.9%, Hb 11.3 mg/dl,

  WBC 9,370 /mm^3 (N 18, L 72, M 4, E 5,B 1),

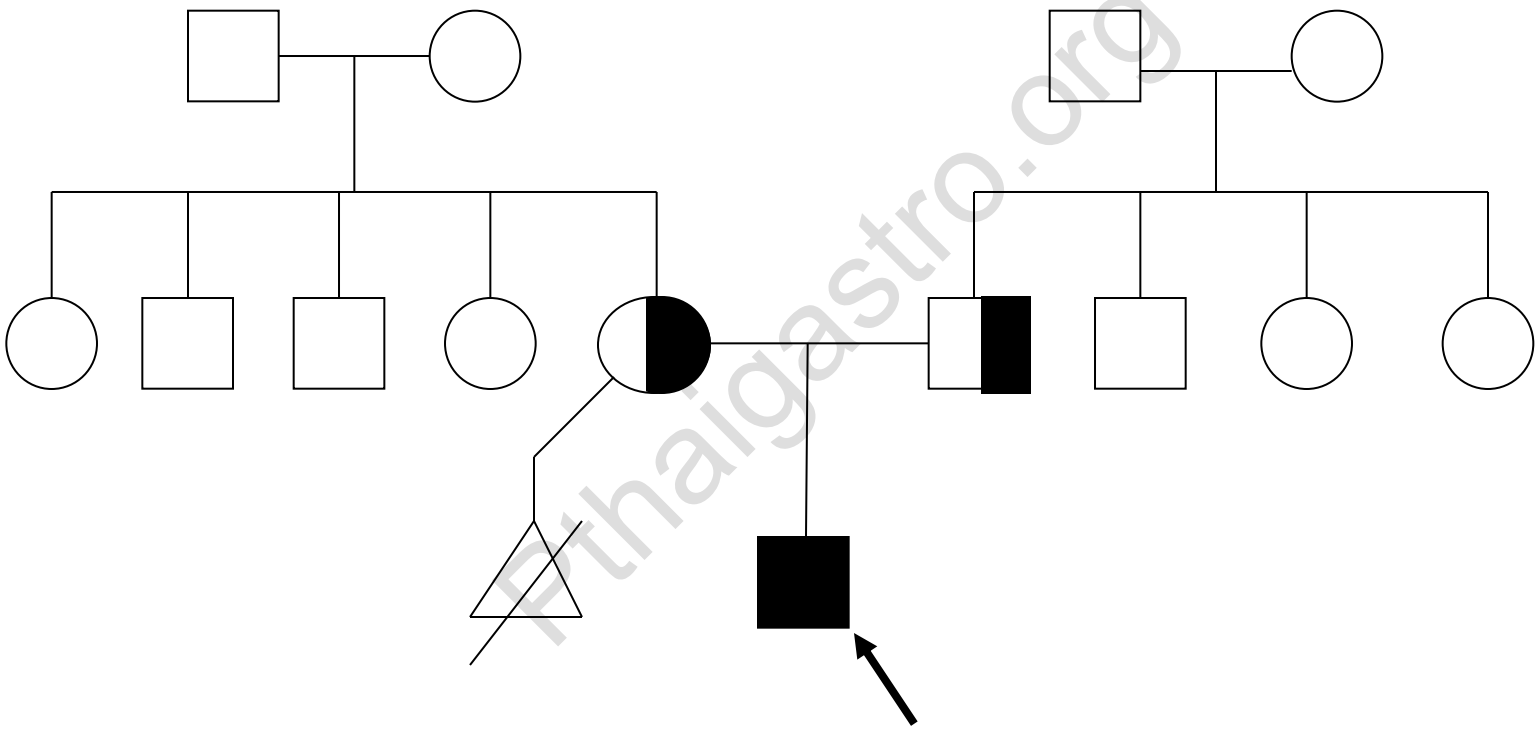
  Platelet 511,000/ mm^3

  (MCV 77, MCH 25.7, MCHC 33.3, RDW 12.2)

- **LFT :** Alb 4.5 , Glob 1.2, TB 28.9, DB 0.5 ,

  AST 34 , ALT 33 , ALP 241, GGT 31

Pedigree



Treatment

- On single phototherapy x 1 day
- Start Phenobarbital 4.3 MKD
- Before discharge → MB 26 mg%

Current status aged 9 month (22/06/54)

- On home phototherapy (blue lights x 6)

with phenobarbital (4.3 MKD)

- **LFT :** TB 21.44, DB 0.39, AST 38, ALT 41, ALP 274

Crigler-Najjar type I

- Complete deficiency of bilirubin-UDP-glucuronosyltransferase.
- Infant who develop persistent jaundice due to unconjugated bilirubin within the first few days after birth.
- Serun bilirubin range from 20 to 25 mg/dl and can be as high as 50 mg/dl.
- Stool color is normal
- Other liver function test are normal.

Crigler-Najjar type II

- Partial deficiency of of bilirubin-UDP-glucuronosyltransferase.
- All patients were clinically normal. Icterus.
- Serum bilirubin < 20 mg/dl, but can rise to levels as high as 40 mg/dl during fasting or intercurrent illness.

Diagnosis of Crigler-Najjar

- Administration of phenobarbitals.
- Chromatographic analysis of bile collected from duodenum.
- DNA extracted from peripheral blood leukocytes, buccal scraping or any other tissue.
- Genetic analysis.

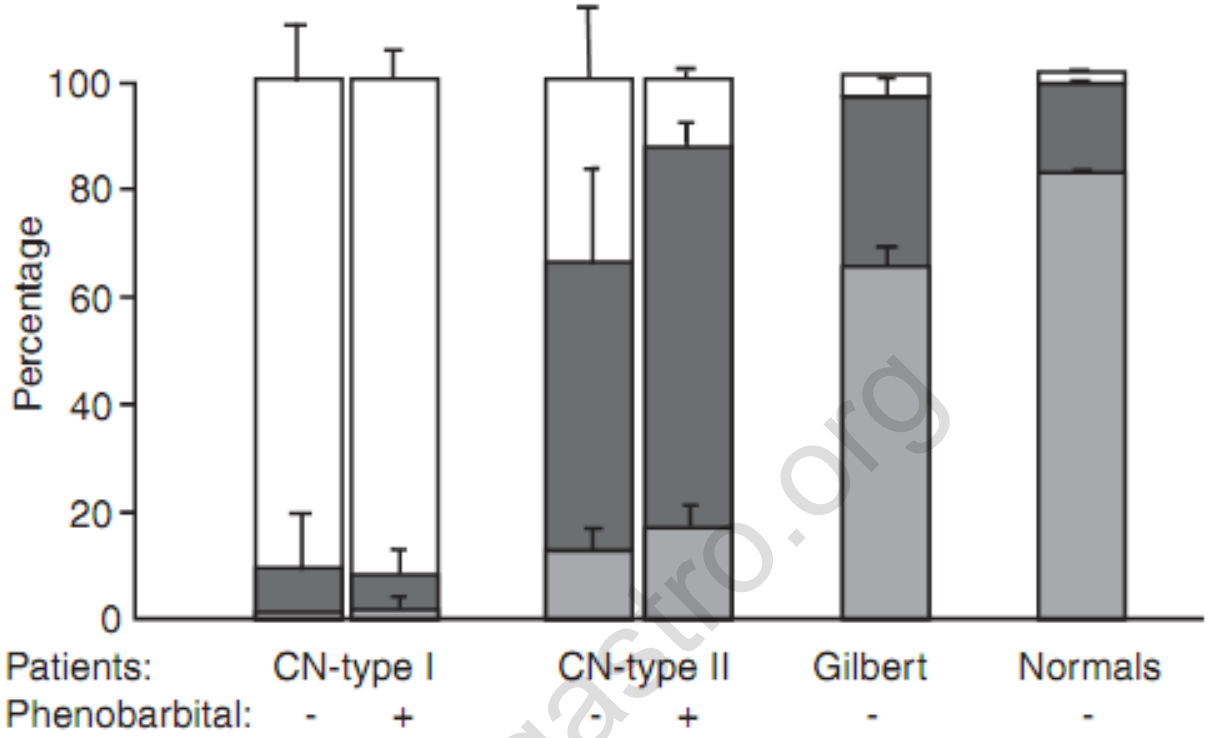


FIGURE 55.5-4 Bile pigment composition in bile from normal (n = 8), Crigler-Najjar (CN) syndrome type I (n = 3), CN type II (n = 3), and Gilbert syndrome (n = 16) patients, receiving (+) or not receiving (–) phenobarbital. Relative bile pigment composition is indicated in the vertical columns as a percentage of the total ± SD. Shading: white = unconjugated bilirubin; intermediate = bilirubin monoconjugate; dark = bilirubin diconjugate. Reproduced with permission from Sinaasappel M and Jansen PL.[49]

Glenn RG. Bilirubin metabolism. Pediatric gastrointestinal disease. 5th edition , 2008

Treatment Crigler-Najjar Type I

- Exchange transfusions
- Life-long phototherapy : 10-12 hr. of phototherapy per 24 hr.
- Tin-protoporphyrin(or Zinc-mesoporphyrin)
- Definite treatment : liver transplantation.
- Hepatocyte transplantation
- Gene therapy

Towards Liver-Directed Gene Therapy for Crigler-Najjar Syndrome

Paula S. Montenegro Miranda and Piter J. Bosma*

AMC Liver Center, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands

Abstract: Crigler-Najjar (CN) syndrome is a recessive inherited disorder caused by deficiency of uridine diphosphoglucuronosyl transferase 1A1. This hepatic enzyme catalyzes the glucuronidation of bilirubin, an essential step in excretion into bile of this neurotoxic compound. As a result, CN patients suffer from severe unconjugated hyperbilirubinemia and are at risk of bilirubin encephalopathy. Over the last decades *ex vivo* and *in vivo* gene therapy using viral and non-viral vectors has been used to correct hyperbilirubinemia in the relevant animal model for CN syndrome, the Gunn rat. Several of these approaches did result in long-term correction of serum bilirubin levels in this animal model. However, none have been translated into a clinical trial.

In this review we will recapitulate the strategies used and discuss their suitability for clinical application in the near future. We will also address specific safety measures in the gene therapy protocol needed to prevent adverse effects such as bilirubin toxicity. Since CN seems an ideal model for other monogenetic inherited metabolic liver disorders, development of liver-directed gene-therapy has relevance beyond this rare disease.

Keywords: Bilirubin, UGT1A1, Gunn rat, Adenovirus, Retrovirus, Lentivirus, AAV, Non-viral vectors.

Treatment of Crigler-Najjar Syndrome Type 1 by Hepatic Progenitor Cell Transplantation: A Simple Procedure for Management of Hyperbilirubinemia

A.A. Khan, N. Parveen, V.S. Mahaboob, A. Rajendraprasad, H.R. Ravindraprakash, J. Venkateswarlu, P. Rao, G. Pande, M. Lakshmi Narusu, M.N. Khaja, R. Pramila, A. Habeeb, and C.M. Habibullah

ABSTRACT

Crigler-Najjar Syndrome (CNS) is characterized by mild, chronic unconjugated hyperbilirubinemia resulting from an autosomal-recessive inherited deficiency of hepatic uridine/diphosphoglucuronate-glucuronosyl transferace 1Al since birth. Herein we have reported a confirmed case of CNS type 1 in a 2-year-old girl with an unconjugated hyperbilirubinemia (>30 mg/dL) treated by hepatic progenitor cell infusion through the hepatic artery. No procedure-related complications were encountered. No kernicterus was observed. The total bilirubin started falling at 10 days after cell infusion. Two months after cell infusion the bilirubin fell from 29.0 to 16 mg/dL, with the conjugated bilirubin increasing approximately fivefold, the unconjugated bilirubin decreasing nearly twofold, and the SGPT also decreasing from 210 U/L to 64 U/L. This study demonstrated the efficacy of hepatic progenitor cells to manage hyperbilirubinemia in these patients. As the procedure is simple and the patient has tolerated the cell therapy, infusion can be repeated as required to manage hyperbilirubinemia, which often causes lethal kernicterus. This study was developed to assess the safety, feasibility, and efficacy of hepatic progenitor cell transplantation in a child with CNS type 1.

Transplantation Proceedings, 40, 1148–1150 (2008)

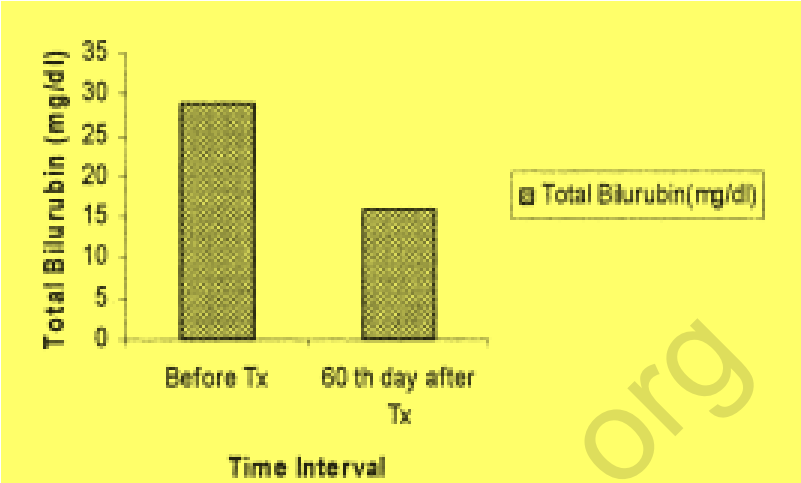


Fig 1. Bilirubin estimation (mg/dL).

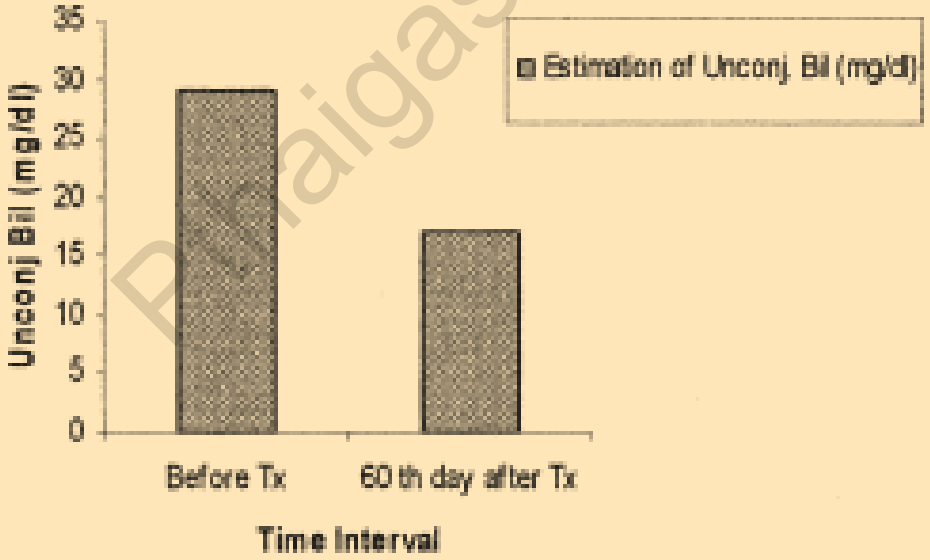
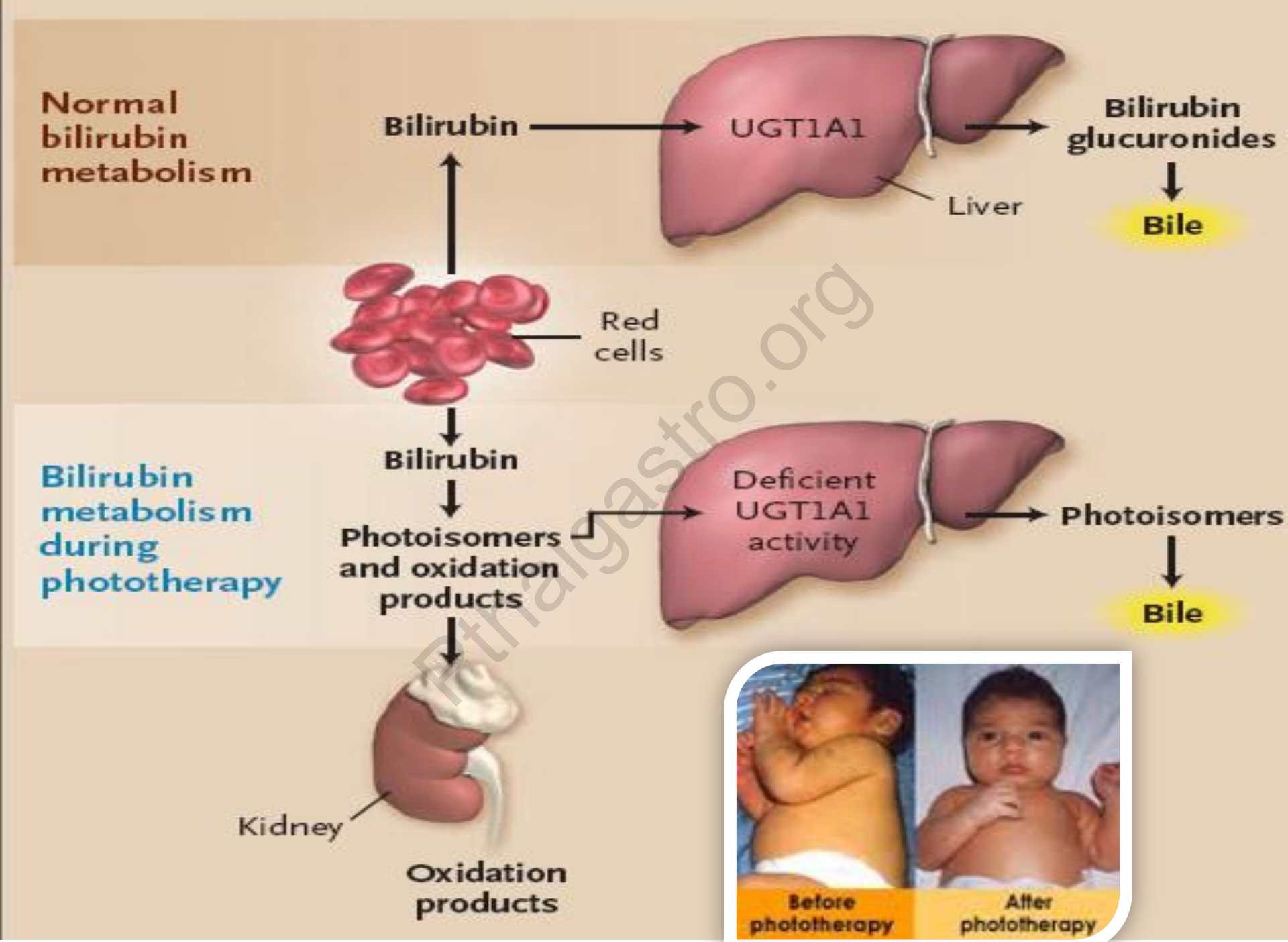


Fig 3. Estimation of unconjugated bilirubin (mg/dL).

Treatment Crigler-Najjar Type II

- Phenobarbital (2-4 mg/kg/day) 2 to 3 times/day



Phototherapy for Neonatal Jaundice. ; M. Jeffrey Maisels.

Parameter	Gilbert	CN I	CN II	Dubin-Johnson	Rotors
Incidence	6-12%	Very rare	Uncommon	Uncommon	Rare
Gene affected	*UGT1A1*	*UGT1A1*	*UGT1A1*	*MRP2*	unknown
Metabolic defect	↓ Bilirubin conjugation	No bilirubin conjugation	↓↓ Bilirubin conjugation	Impaired canalicular export of conjugated bilirubin	Impaired canalicular export of conjugated bilirubin
Serum bilirubin (mg/dl)	≤ 3 in absence of fasting or hemolysis, almost all unconjugated	Usually >20 (17-50), all unconjugated	Usually <20 (6-45), almost unconjugated	Usually <7, about half conjugated	Usually <7, about half conjugated

Parameter	Gilbert	CN I	CN II	Dubin-Johnson	Rotors
Liver histology	Usually normal, occasional ↑ lipofuscin	Normal	Normal	Coarse pigment in centrilobular hepatocyte	Normal
Other disinguishing features	↓ Bilirubin concentratiion with PB	No response to PB	↓ Bilirubin concentratiion with PB	↑ Bilirubin conc. With estrogen; ↑ ↑ urinary coproporphyrin I/III ratio; Slow BSP elimination kinetics with secondary rise	Mild ↑ urinary coproporphyrin I/III ratio, very slow BSP elimination kinetics without secondary rise
Prognosis	Normal	Death in infancy if untreated	Usually normal	Normal	Normal
Treatment	None	Phototherapy as a bridge to liver transplantation	PB for ↑↑ bilirubin conc.	Avoid estrogen	Non available

Ref.Steven D.Lidofsky. Sleisenger and Fordtran's gastrointestinal and liver disease,9th ed.2010 P.332