Case Report

Crigler-Najjar Syndrome Type I with Severe Hyperbilirubinemia and Respiratory Complications in a Child

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ABSTRACT

Background: Crigler-Najjar Syndrome Type I (CNS-1) is a rare inherited metabolic disorder characterized by severe unconjugated hyperbilirubinemia and risk of neurological complications. Children with CNS-1 often require multidisciplinary care, particularly when complicated by infections.

Case Presentation: A 5-year-old male, third-born to second-degree consanguineously married parents, presented with fever, cough, and cold for 2 days. He had a history of CNS-1, global developmental delay, spastic quadriplegia, partial immunization, and neonatal jaundice requiring NICU admission. On examination, he was drowsy, icteric, and in respiratory distress with grunting, stridor, and retractions. CNS examination revealed increased tone in all limbs. Laboratory tests showed severe anemia (Hb 6.19 g/dL), and being managed with PRBC transfusion. Management included Oseltamivir for suspected viral infection, antibiotics, nebulization, chest physiotherapy, oxygen therapy, and gradual transition from OG to oral feeds. ENT evaluation was advised due to stridor; though direct laryngoscopy was not consented. Hearing and ophthalmology assessments were normal. The child improved clinically and was stable at discharge.

Conclusion: This case highlights the importance of multidisciplinary care, family counseling, and regular follow-up in managing children with rare metabolic disorders like CNS-1, especially when complicated by respiratory infections.

Keywords: Crigler-Najjar Syndrome Type I, Global Developmental Delay, Spastic Quadriplegia, Pediatric Respiratory Infection, Multidisciplinary Care, Rare Metabolic Disorder, Anemia.

INTRODUCTION

Crigler–Najjar syndrome (CNS) represents a classic example of an inborn error of metabolism (IEM) and is an ultra-rare autosomal recessive disorder, occurring in fewer than one per million live births. It results from biallelic mutations in the *UGT1A1* gene, which encodes uridine 5'-diphosphate glucuronosyltransferase (UGT1A1). This enzyme catalyzes the glucuronidation of unconjugated Z, Z-bilirubin, primarily producing diglucuronides with smaller amounts of monoglucuronides. Loss or reduction in this pathway leads to pathological accumulation of neurotoxic unconjugated bilirubin in plasma and tissues[1–3].

Mutation in *UGT1A1* can give rise to different clinical entities, most notably Gilbert syndrome and Crigler–Najjar syndrome. The distinction depends largely on the residual activity of UGT1A1 and its inducibility by phenobarbital. In Gilbert syndrome, residual enzyme activity is typically above 20–30%, with only mild elevations in total bilirubin. In contrast, Crigler–Najjar syndrome is divided into two subtypes: Type 2, where enzyme activity is reduced to about 4–10%, and Type 1, in which UGT1A1 activity is absent. These differences explain the much higher serum bilirubin levels observed in CNS compared to Gilbert syndrome[4].

Bilirubin is produced during erythrocyte breakdown and is initially released in its unconjugated form. In healthy individuals, unconjugated bilirubin is transported to the liver, where UGT1A1 mediates conjugation, making it water soluble and allowing its excretion into bile.

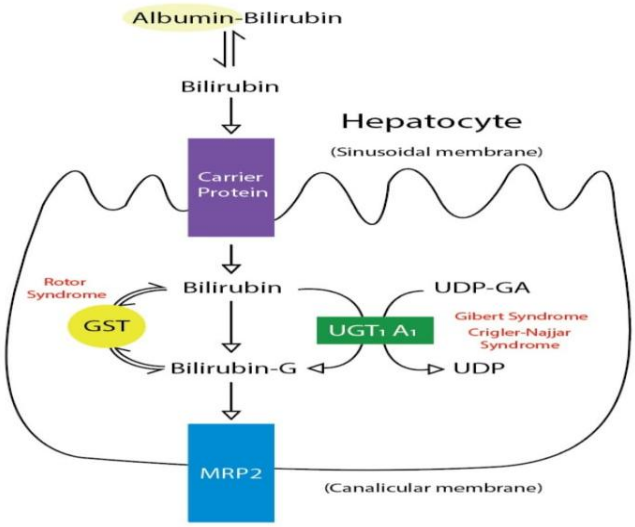

Figure 1: Schematic representation of bilirubin metabolism within the hepatocyte highlighting the role of the UGT1A1 enzyme. In Crigler–Najjar Syndrome Type I, complete absence or dysfunction of UGT1A1 impairs the conjugation of bilirubin with glucuronic acid, leading to severe unconjugated hyperbilirubinemia. The diagram also illustrates associated defects seen in related syndromes such as Gilbert, Rotor, and Dubin–Johnson syndromes.

In CNS, impaired or absent conjugation results in unconjugated bilirubin accumulation, which exceeds albumin's binding capacity. Although about 99% of unconjugated bilirubin normally binds to albumin and remains unable to cross the blood–brain barrier, the unbound fraction readily enters the central nervous system. This free bilirubin deposits in neuronal tissue, leading to bilirubin-induced neurologic dysfunction, including seizures, developmental delay and in severe cases, kernicterus. If untreated, this accumulation can result in irreversible neurological injury and life-threatening complications[5-7].

CASE REPORT

Demographic & Chief Complaints:

A 5-year old male child, the third-born to a second-degree consanguineous couple, was admitted to the Pediatric Department at the Karnataka Institute of Medical Sciences and Research Institute (KIMSRI), Hubballi. He presented with a two-day history of fever, cough and cold and was noted to have severe anemia. There was no associated history of loose stools, reduced urine output, abdominal pain, abnormal limb movements, vomiting or rashes.

The child is a known case of Crigler–Najjar Syndrome Type I with seizure disorder. He has had multiple hospital admissions for similar complaints, including one at the age of one year. Two days prior to the current admission, he was treated at Dharwad Civil Hospital and discharged, making this his fourth hospitalization at KIMSRI.

He was born to a second-degree consanguineous couple who have three children — one daughter and two sons. His elder sibling, a seven-year-old girl, has a history of similar complaints suggestive of an inherited metabolic disorder.

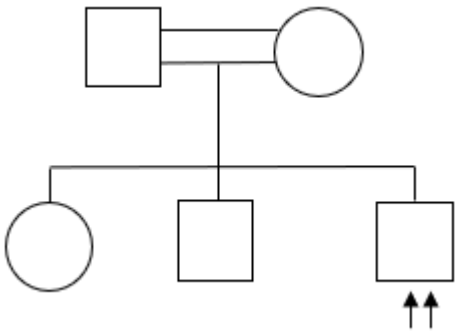

Figure 2: Family history

The antenatal history was unremarkable, with the mother being booked and fully immunized. Delivery was carried out by elective lower segment cesarean section (LSCS) at 39 weeks due to a previous LSCS. The baby cried immediately after birth and weighed 2.54 kg.

On day 10 of life, the infant developed jaundice with yellowish discoloration of the skin and sclera. He was admitted to the NICU, where he received phototherapy for approximately one month. Subsequent genetic testing confirmed Crigler–Najjar Syndrome Type I, showing *UGT1A1* polymorphism (genotype 28/28, TA repeats 7/7), consistent with markedly reduced glucuronidation activity.

The child received initial immunizations with OPV, Hepatitis B and DPT vaccine, but no further vaccinations were administered due to the underlying illness. Developmental assessment revealed global developmental delay, with absent neck holding, closed fist posture, the ability to wave bye-bye and use of bisyllables such as "dada" and "appa."

Table 1: Diet History.

Food items	Taken quantity	Energy / calories	Proteins (grams)
Idli+sambar+chutney	2-3	200	6
1 Chapathi+veg curry	1+1	178	2
1 cup rice+dhal	1+1	278	4
1 Chapathi+veg curry	1+1	178	2
Other nutrients		151	5.8

His medication history included long-term use of Levetiracetam syrup (50 mg/kg/day BD), Gabapentin 100 mg once daily at bedtime, Clonazepam 0.25 mg twice daily, Phenobarbitone 2 mg once daily and Trihexyphenidyl 2 mg once daily.

EXAMINATION FINDINGS

On admission, the child's vital parameters were as follows: temperature 38.7 °C indicating fever, pulse rate 147 beats per minute consistent with tachycardia, respiratory rate 50 breaths per minute suggestive of tachypnea, blood pressure 90/60 mmHg which was on the lower side of normal and a random blood sugar of 166 mg/dL showing mild hyperglycemia.

Table 2: Vital Parameters

Parameter	Observed valve	Normal valve	Interpretation
Temp	38.7 C	36.5-37.5 C	Fever
PR	147 B/M	80-120 B/M	Tachycardia
RR	50 B/M	20-30B/M	Tachypnea
BP	90/60 mm/Hg	95-105/60-70	Decreased BP
GRBS	166 mg/dl	<140 mg/dl	Mild Hyperglycemia

General physical examination revealed the presence of pallor and icterus. Cyanosis, clubbing, lymphadenopathy and edema were not observed. Inspiratory stridor was noted. Anthropometric measurements showed a height of 90 cm (–2 SD), weight of 12.5 kg (–2 to –3 SD) and a BMI of 15.4 indicating the child was stunted and underweight.

Table 3: Anthropometry

Parameters	Observed	Expected	Interpretation
Height	90 cm	108.9	-2 SD
Weight	12.5	17.1	-2SD to -3SD
BMI	15.4	14.7	Normal

Impression: Stunted and Underweight Child

On systemic examination, the abdomen was soft with the liver palpable 2 cm below the right costal margin, the spleen was not palpable. Neurological assessment revealed increased tone in all four limbs, brisk reflexes, bilateral plantar flexor response and features of spastic quadriplegia. There were no signs of meningeal irritation. Cardiovascular examination demonstrated normal heart sounds (S1 and S2) with no murmurs. Respiratory examination showed decreased bilateral air entry with suprasternal and subcostal retractions; the trachea was centrally placed. Cranial nerves were mostly intact, although hearing could not be assessed.

Laboratory Data

Genetic analysis performed at 2 months of age confirmed the diagnosis of Crigler–Najjar Syndrome Type I, with *UGT1A1* polymorphism (genotype 28/28, TA repeats 7/7), consistent with markedly reduced glucuronidation activity (<70%).

Investigations performed during the current admission (23rd and 29th May 2025) showed the following results:

- Hemoglobin improved from 6.16 g/dL to 9.62 g/dL following treatment.
- Total bilirubin was markedly elevated at 24.4 mg/dL on admission and decreased to 7.72 mg/dL after therapy, confirming severe unconjugated hyperbilirubinemia.
- Direct bilirubin rose slightly from 0.1 mg/dL to 1.9 mg/dL, supporting unconjugated predominance.
- Arterial blood gases showed a pO_2 of 72 mmHg, indicating hypoxemia.
- Serum electrolytes revealed hypokalemia (K^+ 3.1 mEq/L) and slightly low chloride (97.6 mEq/L).
- Creatinine, bicarbonate, and pCO_2 levels were within normal limits.

Management

During hospitalization, the patient was treated with IV Levofloxacin (50 mg twice daily for 7–10 days) and IV Ceftriaxone (500 mg twice daily for 7–10 days) for bronchopneumonia. Seizures were managed with IV Midazolam (1 mg, given as needed). Antipyretic therapy included oral Indomethacin (0.3 ml three times daily) and oral Nimesulide (1 ml twice daily). Long-term seizure prophylaxis was continued with oral Phenobarbitone (30 mg once daily), while oral Gabapentin (100 mg at bedtime) was prescribed for neuropathic pain and spasticity. Nutritional support was provided in the form of calcium and multivitamin supplementation. At the time of discharge, the patient was prescribed the following medications: Levetiracetam syrup (50 mg/kg/day, twice daily), Gabapentin 100 mg once daily at bedtime, Phenobarbitone 2 mg once daily, Clonazepam 0.25 mg twice daily, along with calcium and multivitamin syrups for supportive care.

DISCUSSION

This case highlights the classical phenotype of Crigler–Najjar Syndrome Type I (CNS-I), characterized by severe unconjugated hyperbilirubinemia, early-onset jaundice in the neonatal period and progressive neurological complications. The diagnosis in patient was genetically confirmed through identification of *UGT1A1* 28/28 polymorphism with TA repeats (7/7), consistent with markedly reduced or absent glucuronidation activity

Table 4: Laboratory Investigation

Test Name	Observed Value	Normal Value	Interpretation
Hemoglobin	6.16 g/dL → 9.62 g/dL	11.0 – 14.0 g/dL	Severe anemia initially, improved after treatment
Total Bilirubin	24.40 mg/dL → 7.72 mg/dL	0.2 – 1.2 mg/dL	Very high, diagnostic of CNS-1; decreasing with management
Direct Bilirubin	0.1 mg/dL → 1.9 mg/dL	0 – 0.2 mg/dL	Unconjugated predominance; still elevated
Uric Acid	3.1 mg/dL	3.5 – 7.2 mg/dL	Within normal range
Potassium	3.1 mEq/L	3.5 – 5.0 mEq/L	Hypokalemia (needs correction)
pO_2	72 mmHg	75 – 100 mmHg	Mild hypoxemia
HCO_3	24 mEq/L	22 – 26 mEq/L	Normal
Creatinine	0.2 mg/dL	0.3 – 0.7 mg/dL	Normal renal function

Table 5: Treatment Management

Drug (Generic)	Frequency	Dose	Route	Duration	Indication
IV Levofloxacin	BD	50 mg	IV	7-10 days	Broad-spectrum antibiotic for bronchopneumonia
IV Midazolam	SOS	1 mg	IV	As needed	Sedation/seizure control
IV Ceftriaxone	BD	500 mg	IV	7-10 days	Broad-spectrum antibiotic for bronchopneumonia
Oral Indomethacin	TD	0.3 ml	Oral		Fever/pain management
Oral Nimesulide	BD	1 ml	Oral		NSAID for fever/pain
Oral Phenobarbitone	OD	30 mg	Oral	Long-term	Enzyme induction, seizure prophylaxis
Oral Gabapentin	HS	1 tab	Oral	Long-term	Neuropathic pain/spasticity

The child developed kernicterus, which manifested clinically as global developmental delay (GDD) and spastic quadriplegia—both recognized long-term sequelae of chronic bilirubin neurotoxicity. These findings are in line with previously published reports, where untreated or inadequately treated CNS-I often leads to irreversible neurological damage.

Unlike CNS Type II or Gilbert syndrome, CNS-I does not respond to phenobarbital therapy, as enzyme activity is absent rather than partially preserved. Therefore, therapeutic strategies are largely limited to supportive measures such as phototherapy, exchange transfusions, anticonvulsant therapy for seizure control, antibiotics for intercurrent infections and nutritional supplementation. While these interventions provide temporary relief, they do not halt disease progression.

The repeated episodes of bronchopneumonia in this child reflect increased susceptibility to infections, likely compounded by neurological impairment, chronic malnutrition, and reduced immunity. Such complications are frequently observed in children with metabolic and neurodevelopmental disorders.

Currently**,** liver transplantation remains the only definitive therapy for CNS-I, as it restores glucuronidation activity and prevents further bilirubin neurotoxicity. However, socioeconomic limitations often prevent timely access to transplantation in low-resource settings, including the present case. Published literature supports that early referral to transplant centers significantly improves long-term survival and neurodevelopmental outcomes, underscoring the importance of timely intervention.

CONCLUSION

The case describes a 5-year-old male child with Crigler–Najjar Syndrome Type I, confirmed by *UGT1A1* polymorphism, who presented with recurrent episodes of fever, anemia, and respiratory infections on the background of severe unconjugated hyperbilirubinemia. Despite multiple hospitalizations and long-term supportive therapy, the child developed significant complications including global developmental delay, spastic quadriplegia and seizure disorder, reflecting the progressive neurological damage caused by chronic bilirubin encephalopathy.

Management during admission focused on controlling bronchopneumonia, stabilizing anemia, managing seizures and providing nutritional support. While bilirubin levels improved transiently with therapy, the persistence of hyperbilirubinemia underscores the limitations of supportive treatment in CNS-I. As seen in this case, phenobarbital and other conservative measures cannot prevent disease progression, and recurrent infections further worsen morbidity due to compromised nutrition and neurological status.

This report emphasizes the need for early diagnosis, regular monitoring, and timely referral for liver transplantation, the only curative option for CNS-I. In addition, family counseling and genetic screening play a critical role in preventing recurrence in populations with consanguinity. Strengthening access to definitive care and long-term multidisciplinary follow-up is essential to improve outcomes in children affected by this devastating disorder.

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REFERENCES

1. Jansen PLM. Diagnosis and management of Crigler-Najjar syndrome. European Journal of Pediatrics. 1999 Jan 1;158(S2): S089–94.
2. Dhawan A, Lawlor MW, Mazariegos GV, McKiernan PJ, Squires JE, Strauss KA, et al. Disease burden of Crigler–Najjar syndrome: Systematic review and future perspectives. 2020 Apr 1;35(4):530–43.
3. Aronson SJ, Junge N, Mediha Trabelsi, Wided Kelmemi, Hubert A, Brigatti KW, et al. Disease burden and management of Crigler-Najjar syndrome: Report of a world registry. 2022 Mar 11;42(7):1593–604
4. Strauss KA. Crigler najjar syndrome type 1: pathophysiology, natural history and therapeutic frontier. Straiss KA, editor. AASLE. 2020;71(6).
5. Bhandari J, Thada PK, Shah M, Yadav D. Crigler-Najjar Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. [updated 2024 Feb 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562171/
6. Adarsh et al. Case study highlighting neonatal metabolic complications in rare syndromes. *World J Pharm Pharm Sci*. 2025;14(7):662–669
7. Adarsh et al. Niemann–Pick disease case report: insights into rare metabolic storage disorders. *Indian J Med Case Rep*. 2024; 13:5–10