JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.35229
J Inonu Liver Transpl Inst 2024;2(2):85–87

Case Report

Living Donor Liver Transplantation in Patients with Crigler-Najjar Syndrome Type 1: Report of Three Cases

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Abstract

Crigler-Najjar syndrome (CNS) type 1 is a rare autosomal recessive disorder caused by mutations in the UGT1A1 gene, leading to a complete deficiency of the enzyme uridine diphosphate-glucuronosyltransferase (UGT1A1). This enzyme deficiency results in severe unconjugated hyperbilirubinemia, which poses a high risk of neurological complications, particularly kernicterus, if left untreated. While phototherapy provides temporary relief in early childhood, its diminishing effectiveness over time requires liver transplantation (LT) as the only definitive treatment. In this report, we present three pediatric cases of CNS type 1 treated successfully with living donor liver transplantation (LDLT). The first case, an 11-year-old girl, presented severe jaundice and neurological impairment but showed significant improvement in bilirubin levels and neurological symptoms after transplantation. The second case, a 12-year-old boy, had persistently high bilirubin levels despite phototherapy, which normalized after LDLT. The third case, an 11- month-old infant without prior treatment, also achieved complete normalization of bilirubin levels after transplantation. These cases demonstrate that LDLT is highly effective in preventing kernicterus, normalizing bilirubin levels, and improving clinical outcomes in patients with type 1 CNS. Long-term post-transplant care, including immunosuppressive therapy and regular follow- up, remains essential for optimal management and patient well-being.

Keywords: Autosomal recessive, crigler-najjar syndrome, liver transplant, orthotopic liver transplantation, ugt1a1, unconjugated bilirubin.

Please cite this article as "Guzelaltuncekic E, Ayyildiz Civan H, Sari F, Sonmez Topcu F, Toprak HI, Tuncer A, et al. Living Donor Liver Transplantation in Patients with Crigler-Najjar Syndrome Type 1: Report of Three Cases. J Inonu Liver Transpl Inst 2024;2(2):85–87".

Crigler-Najjar syndrome (CNS) is a rare autosomal recessive disorder characterized by elevated levels of unconjugated bilirubin due to mutations in the UGT1A1 gene located on chromosome 2.

The syndrome is classified into two types: CNS type 1 and CNS type 2. CNS type 1, the more severe form of the CNS, manifests shortly after birth and leads to persistently high bilirubin levels throughout life. Patients with CNS type 1 are at high risk for bilirubin-induced neurological dysfunction (BIND), ranging from mild reversible impairments to severe irreversible encephalopathy known as kernicterus.

The primary cause of CNS type 1 is the complete absence of hepatic uridine diphosphate- glucuronosyltransferase (UGT1A1) activity, leading to accumulation of unconjugated bilirubin in the bloodstream. This condition is typically diagnosed by detecting elevated unconjugated bilirubin levels in serum or by genetic analysis that identifies mutations in the UGT1A1 gene.[4,5] The global incidence of

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Submitted Date: 23.08.2024 **Revised Date:** 18.09.2024 **Accepted Date:** 18.09.2024 **Available Online Date:** 09.10.2024

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CNS type 1 is estimated at 1 in 1,000,000 live births, with a higher prevalence in populations where consanguineous marriages are common.[1,2]

Treatment Options

For patients with CNS type 1, daily phototherapy (PT) is the main initial treatment, particularly in the neonatal period. Phototherapy helps convert unconjugated bilirubin into a more water-soluble form, allowing it to be excreted through the bile. However, the effectiveness of phototherapy decreases as the skin thickens with age, leading to a reduced ability to lower bilirubin levels. Plasmapheresis and exchange transfusions can provide temporary relief by mechanically removing unconjugated bilirubin from the circulation, but these are not long-term viable options. Pharmacological approaches, such as enzyme inducers such as phenobarbital, are ineffective in CNS type 1 due to a complete lack of enzyme activity.

Liver transplantation (LT) is the only definitive treatment for CNS type 1.[3] Transplanted livers provide the missing UGT1A1 enzyme, allowing for proper conjugation and excretion of bilirubin. Studies have shown that liver transplantation not only normalizes bilirubin levels, but also reduces the risk of long-term neurological complications. However, LT is associated with lifelong immunosuppressive therapy and the risk of posttransplant complications.

This report presents three cases of pediatric patients with CNS type 1 who successfully underwent living donor liver transplantation (LDLT), resulting in significant clinical improvements.

Case Report

Case 1 — An 11-year-old Palestinian girl, weighing 30 kg and measuring 131 cm in height, presented persistent jaundice, delayed speech, and walking difficulties. Laboratory results showed an indirect bilirubin level of 21.1 mg/dL, while liver function tests, thyroid function tests, and urinalysis were normal. No glucose-6-phosphate dehydrogenase (G6PDH) or pyruvate kinase deficiency was detected, and there was no ABO or Rh incompatibility between the mother and the patient. Genetic analysis revealed a homozygous mutation in the UGT1A1 gene, confirming the diagnosis of Crigler-Najjar syndrome type 1 (CNS1).

The patient had been receiving 8 hours of home phototherapy daily for 10 years, but bilirubin levels remained elevated at 24.7 mg/dL (indirect bilirubin: 24.1 mg/dL, direct bilirubin: 0.6 mg/dL) when admitted for liver transplantation. Abdominal CT and brain magnetic resonance imaging did not show pathological findings. She underwent a living donor left lobe liver transplantation (LDLT) from her mother. The surgery involved duct-to-duct anastomosis of the bile duct and placement of a 5F trans-cystic feeding catheter. The patient was discharged on postoperative day 11. She experienced postoperative bacterial cholangitis, which was successfully treated with antibiotics. At the 4-month follow-up, the biliary catheter was removed and her total bilirubin level had decreased to 0.5 mg/dL (direct bilirubin: 0.2 mg/dL, indirect bilirubin: 0.3 mg/dL). Her bilirubin levels remained stable under immunosuppressive treatment.

Case 2 — A 12-year-old Turkish boy, weighing 37 kg and standing 153 cm tall, presented with an indirect bilirubin level of 28.2 mg/dL. Liver and thyroid function tests were normal, and no G6PDH or pyruvate kinase deficiency was found. There was ABO and Rh incompatibility between the patient and his mother. Despite long-term phototherapy, patient bilirubin levels remained elevated. Genetic testing revealed a homozygous mutation in the UGT1A1 gene, confirming the diagnosis of CNS1.

The patient underwent LDLT from his aunt, a blood-matched donor. During surgery, two arteries and a single bile duct were identified. The bile duct was duct-to-duct anastomosed, and a trans- coledochal 5F feeding catheter was placed. He was discharged on postoperative day 8. At 4 months of follow-up, the biliary catheter was removed and his total bilirubin level had decreased to 0.9 mg/dL (direct bilirubin: 0.3 mg/dL, indirect bilirubin: 0.6 mg/dL). His bilirubin levels remained stable under immunosuppressive treatment.

Case 3 — An 11-month-old Jordanian boy, weighing 9.8 kg and measuring 72 cm in height, had a history of persistent indirect hyperbilirubinemia since birth. The older sister of the patient had died at the age of 6 years due to jaundice, although the cause was not determined. Liver enzymes were normal, but total bilirubin was elevated at 28 mg/dL (direct bilirubin: 0.8 mg/dL). The patient had not received phototherapy or plasma exchange therapy prior to transplantation. Genetic testing identified a homozygous mutation in the UGT1A1 gene, confirming CNS1.

He underwent a reduced-size LDLT from his father. The surgery was uneventful, and the patient was discharged on postoperative day 10. At 4 months of follow-up, the biliary catheter was removed and his total bilirubin had decreased to 0.5 mg / dl (direct bilirubin: 0.3 mg / dl, indirect bilirubin: 0.2 mg/dL). His bilirubin levels remained stable under immunosuppressive treatment.

Discussion

Crigler-Najjar syndrome (CNS) is a rare congenital condition that results in severe unconjugated hyperbilirubinemia due to the absence or severe reduction of UGT1A1 enzyme activity. The distinction between CNS type 1 and type

2 is critical, as it dictates treatment approaches. CNS type 1 patients lack any UGT1A1 enzyme activity, leading to dangerously high levels of bilirubin that can cause irreversible neurological damage if not managed appropriately. In contrast, patients with CNS type 2 retain partial enzyme activity and respond well to pharmacological treatments, such as phenobarbital, which effectively reduces bilirubin levels in CNS type 2 but does not have an effect in CNS type 1.

The management of CNS type 1 is complex, with phototherapy being the mainstay of treatment during early childhood. Although phototherapy can significantly reduce bilirubin levels, its efficacy decreases as the skin thickens with age, making it less effective in older children. Furthermore, prolonged use of phototherapy is not without its complications, including skin damage and the risk of developing resistance to phototherapy.[6,7] For these reasons, liver transplantation (LT) is the only definitive treatment for CNS type 1, providing the missing enzyme necessary for bilirubin conjugation and excretion.

All three cases presented in this report underwent living donor liver transplantation (LDLT) with favorable outcomes. Posttransplant, bilirubin levels normalized in all patients and none required further phototherapy. Although LT is curative for the metabolic defect, long-term management of CNS type 1 patients includes monitoring for potential complications related to immunosuppressive therapy, such as infection and graft rejection. It is important to note that while LT corrects the metabolic defect, the underlying genetic mutation remains and affected individuals may pass the mutation to their offspring.[8,9]

Neurological outcomes in CNS type 1 patients who developed kernicterus prior to transplantation remain a topic of debate.[10] In some cases, LT has been shown to stop the progression of neurological symptoms, while in others, existing neurological damage may persist despite successful transplantation. In our 11-year-old patient, mild improvement in speech and gait was observed after transplantation, suggesting some degree of neurological recovery. However, more research is required to fully understand the potential for neurological improvement in patients with CNS type 1 after LT.

Conclusion

Crigler-Najjar syndrome type 1 is a rare but severe genetic disorder that requires early diagnosis and intervention to prevent irreversible neurological damage, such as kernicterus. While phototherapy provides temporary relief in early childhood, liver transplantation remains the only definitive treatment, as it restores the enzyme necessary for bilirubin conjugation.

Disclosures

Informed consent: Written informed consent was obtained from the parents of the patients for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.G.; Design – H.A.C.; Supervision – A.D.; Materials – F.S.; Data collection &/or processing – F.S.T.; Analysis and/or interpretation – H.İ.T.; Literature search – A.T., E.Ş.; Writing – V.E., E.G., H.A.C.; Critical review – B.Ü.

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