DOI: 10.4274/anatoljmed.2024.77785
Anatol J Gen Med Res 2024;34(2):227-30

CASE REPORT / OLGU SUNUMU

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Liver Transplantation in Crigler-Najjar Syndrome

Crigler-Najjar Sendromunda Karaciğer Nakli

Mirjalal Kazimi[1], Kamran Beydullayev[1], Kanan Asadov[2], Zarifa Yusifli[3], Mehdi Aliyev[4], Madina Abdullayeva[5], Elnur Farajov[6], Aghakishi Yahyayev[7], Shahnaz Jafarova[8], Saida Shindiyeva[1], Aynur Pashayeva[1], Shabnam Gadimaliyeva[6], Haji Rasulzada[1], Safa Vatansever[9]

[1]Department of Surgery and Organ Transplantation, Central Customs Hospital, Baku, Azerbaijan
[2]Departmet of Cardiac Surgery, Central Customs Hospital, Baku, Azerbaijan
[3]Department of Pathology, Central Customs Hospital, Baku, Azerbaijan
[4]Department of Anesthesiology and Intensive Care, Central Customs Hospital, Baku, Azerbaijan
[5]Department of Infectious Diseases and Clinical Microbiology, Central Customs Hospital, Baku, Azerbaijan
[6]Department of Nephrology, Central Customs Hospital, Baku, Azerbaijan
[7]Department of Interventional Radiology, Republic Diagnostic Center, Baku, Azerbaijan
[8]Department of Radiology, Central Customs Hospital, Baku, Azerbaijan
[9]Department of General Surgery, İzmir University of Economics Medical Point Hospital, İzmir, Turkey

Cite as: Kazimi M, Beydullayev K, Asadov K, Yusifli Z, Aliyev M, Abdullayeva M, Farajov E, Yahyayev A, Jafarova S, Shindiyeva S, Pashayeva A, Gadimaliyeva S, Rasulzada H, Vatansever S. Liver Transplantation in Crigler-Najjar Syndrome. Anatol J Gen Med Res. 2024;34(2):227-30

Abstract

Crigler-Najjar syndrome is a rare, inherited disease that causes unconjugated hyperbilirubinemia. Liver transplantation is a definitive treatment option for Crigler-Najjar syndrome. Two patients with Crigler-Najjar syndrome who received liver transplantation are presented in this case report. The first patient who was misdiagnosed with Gilbert's syndrome was a 15-year-old male. He had speech and gait disturbances that partially recovered after liver transplantation. The second patient was a 22-year-old male. He developed liver fibrosis although he had a mild clinical form of the disease. Liver transplantation was successfully performed for both of these patients without significant morbidity.

Keywords: Liver transplantation, Crigler-Najjar syndrome, liver fibrosis

Öz

Crigler-Najjar sendromu, unkonjüge hiperbilirubinemiye neden olan nadir, kalıtsal bir hastalıktır. Karaciğer nakli, Crigler-Najjar sendromu için kesin tedavi sağlayan bir seçenektir. Bu olgu sunumunda Crigler-Najjar sendromu nedeniyle karaciğer nakli yapılan iki hasta sunuldu. Gilbert sendromu olarak yanlış teşhis konulan ilk hasta 15 yaşında bir erkekti. Var olan konuşma ve yürüme bozukluğu karaciğer nakli sonrası kısmi olarak düzeldi. İkinci hasta 22 yaşında erkekti. Hastalığın hafif bir klinik formuna sahip olmasına rağmen, karaciğer fibrozisi gelişmişti. Karaciğer nakli her iki hastaya da önemli bir morbidite olmaksızın başarıyla uygulandı.

Anahtar Kelimeler: Karaciğer nakli, Crigler-Najjar sendromu, karaciğer fibrozisi

Address for Correspondence/Yazışma Adresi: Safa Vatansever MD, Department of General Surgery, İzmir University of Economics Medical Point Hospital, İzmir, Turkey
Phone: +90 232 399 50 50 **E-mail:** safa.vatansever@hotmail.com
ORCID ID: orcid.org/0000-0002-0303-6098

Received/Geliş tarihi: 30.05.2023
Accepted/Kabul tarihi: 16.03.2024

Introduction

Crigler-Najjar syndrome (CNS) is a rare, autosomal recessive disorder characterized by unconjugated hyperbilirubinemia. A mutation in the *UGT1A1* gene located on chromosome 2 causes partial or complete loss of function of the uridine diphosphate-glucuronosyl transferase enzyme, which provides bilirubin glucuronidation. Therefore, severe unconjugated hyperbilirubinemia occurs in the affected individuals[1]. If the level of unconjugated bilirubin rises above the albumin binding capacity, free circulating bilirubin accumulates in lipophilic tissues. This accumulation is particularly important in the brain because brain damage develops in varying severity[2,3].

Phototherapy (PT) is commonly used in CNS patients to lower bilirubin levels. Although it is effective in the initial years of therapy, its effectiveness diminishes over time[1,4]. Thus, most patients with CNS eventually require liver transplantation (LT) at early ages of their life[2]. The mean and median age at transplantation was reported as 9 years, ranging from 0 to 32 years, in different world registries[5,6].

This paper presents two patients with CNS type I who received LT at a relatively late age due to misdiagnosis and lack of medical care.

Case Reports

Case 1

The first patient was a 15-year-old male. His parents were first-degree cousins. His elder brother died of an undiagnosed disease with similar symptoms.

The patient had icteric sclera since the first year of life. However, he was misdiagnosed with Gilbert's syndrome and received no treatment. He had no other complaints until four months ago. He was admitted with speech and gait disturbance that had been present for four months. Upon sequencing the coding exon 5 of UGT1A1, a homozygous c.1381T>C mutation was detected, resulting in a p. W461R substitution at the protein level. He was diagnosed with CNS type I by genetic analysis. Phenobarbital was given to the patient, but the symptoms worsened. He was then referred for LT.

The patient had severe jaundice, and his serum total bilirubin level was 19.6 mg/dL. During his neurological examination, the patient was stuttering and had trouble choosing the right words when speaking. He was walking in an anteflexed position with his knees slightly flexed. His general orientation was impaired. However, his brain magnetic resonance imaging showed no significant abnormalities.

The donor was his 42-year-old mother. No genetic tests were performed before organ donation. The patient underwent live donor liver transplantation (LDLT) with a right liver lobe graft. The early postoperative period was uneventful. The serum total bilirubin level gradually decreased to 0.7 mg/dL starting from 31 mg/dL in the immediate postoperative period. At the end of the 1-year follow-up, liver function was normal and neurological status improved without complete recovery. While the gait disturbance was completely resolved, he still had troubles with his speech.

Case 2

The second patient was a 22-year-old male. His parents were first-degree cousins, similar to the first case. The family history was otherwise uneventful, with no significant systemic diseases.

He had jaundice from birth; however, he had never consulted a doctor before and hence did not receive any treatment. Because of DNA sequence analysis of this patient, the same genetic mutation was detected as in the first case. In addition, liver fibrosis was detected with imaging studies, and the patient was finally referred for LT. He had no neurological symptoms, unlike the previous patient. The serum total bilirubin level was 21.0 mg/dL.

The patient underwent left lobe LDLT. The donor was his 51-year-old father. The early postoperative period was uneventful. The serum total bilirubin level gradually decreased to 1 mg/dL in the early postoperative period; however, it started to rise again up to 20 mg/dL at the postoperative 10th month. Magnetic resonance cholangiopancreatography revealed stenosis in the biliary reconstruction. Percutaneous transhepatic cholangiography was performed to dilate the stenosis, and bilirubin values returned to normal afterward. At the end of the 1-year follow-up, the liver function and neurological status of the patient were normal.

Discussion

CNS is a rare, inherited disease characterized by hyperbilirubinemia. It was first described as "congenital familial non-hemolytic jaundice" in 1952 by Crigler and Najjar[7]. The initial paper consisted of six children with reported 100% mortality, most of whom perished in the early years of their lives[7]. The development of PT provided these

patients with a longer life without neurological disability[8]. Mortality rates decreased to an impressive 7.1% ratio in patients who received adequate and high standard PT, and most of these patients reached adulthood without any signs of encephalopathy[6].

Genetic analysis plays a pivotal role in diagnosing CNS, as it helps clinicians identify specific mutations in the *UGT1A1* gene, guiding personalized treatment plans, and enhancing our understanding of this rare genetic disorder[9]. Both patients were diagnosed by genetic testing.

The study; using a web-based world registry, which included data from 221 CNS patients, and reported PT as the most common treatment. A total of 75 patients among the 132 patients who were offered PT as a monotherapy failed to receive adequate PT due to lack of infrastructure. The reported mortality rate was 7.1% for patients who had sufficient access to PT as opposed to the mortality rate of 62.7% in patients with insufficient access[6]. These results clearly demonstrate the effectiveness of PT.

However, PT has its own limitations. Its efficacy decreases over time because of skin thickening and decreasing body surface area to weight ratio. In addition, the compliance with the treatment decreases over time, as PT sessions last approximately 10-12 hours a day. Daily therapy duration also limits social life and negatively affects quality of life[5,6,8].

Another issue to be considered for treating CNS is liver fibrosis. Liver fibrosis in patients with CNS type I and II has started to be reported in increasing frequency[10-13]. The cause and consequence of fibrosis are not clear[1,13]. In a recent study, Aronson et al.[6] indicated that all patients with liver fibrosis in the cohort were 7 years or older and had a severe form of CNS. In contrast, Schröder et al.[1] reported varying levels of fibrosis, differing in severity regardless of the type of CNS. Only one patient in the current report developed liver fibrosis, despite having a favorable disease course mild enough to live untreated until the age of 22.

LT is a definitive and effective therapy for CNS[5]. A recent single-center retrospective study including 13 CNS patients who underwent LT showed that the overall survival rate was 100%. The graft survival rate for the first LT was 61.5%. Five patients underwent re-transplantation and one patient underwent a second re-transplantation. At the end of a median follow-up period of 10 years, 12 of 13 patients' graft function was normal[1]. In the aforementioned web-based world registry report, 26 patients underwent LT for CNS. LT was curative for all patients. However, the LT-related complication rate was 54%[6]. According to these results, LT offers a definitive curative treatment option for patients with severe CNS.

This report shows that LT is a curative treatment even in cases where treatment is delayed for various reasons. Because liver fibrosis can develop independently of the severity of the disease and clinical findings, liver fibrosis should be a part of the routine evaluation in the follow-up of CNS patients.

Ethics

Informed Consent: Informed consent was obtained from the patients in this report.

Authorship Contributions

Surgical and Medical Practices: M.K., K.B., K.A., Z.Y., M.A., M.Ab., E.F., A.Y., S.J., S.S., A.P., S.G., H.R., Concept: S.V., Design: S.V., Data Collection or Processing: S.S., Analysis or Interpretation: S.V., Literature Search: S.V., Writing: S.V., M.K., K.B., K.A., Z.Y., M.A., M.Ab., E.F., A.Y., S.J., S.S., A.P., S.G., H.R.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Schröder H, Junge N, Herden U, et al. Outcome of liver transplantation and prevalence of liver fibrosis in Crigler-Najjar syndrome. Clin Transplant. 2021;35:e14219.
2. Bortolussi G, Muro AF. Advances in understanding disease mechanisms and potential treatments for Crigler-Najjar syndrome. Expert Opin. Orphan Drugs. 2018;6:425-39.
3. Tcaciuc E, Podurean M, Tcaciuc A. Management of Crigler-Najjar syndrome. Med Pharm Rep. 2021;94(Suppl 1):S64-7.
4. Tu ZH, Shang DS, Jiang JC, et al. Liver transplantation in Crigler-Najjar syndrome type I disease. Hepatobiliary Pancreat Dis Int. 2012;11:545-8.
5. van der Veere CN, Sinaasappel M, McDonagh AF, et al. Current therapy for Crigler-Najjar syndrome type 1: Report of a world registry. Hepatology. 1996;24:311-5.
6. Aronson SJ, Junge N, Trabelsi M, et al. Disease burden and management of Crigler-Najjar syndrome: Report of a world registry. Liver Int. 2022;42:1593-604.
7. Crigler JF, Najjar VA. Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics. 1952;10:169-80.
8. Dhawan A, Lawlor MW, Mazariegos GV, et al. Disease burden of Crigler–Najjar syndrome: Systematic review and future perspectives. Gastroenterol Hepatol. 2020;35:530-43.

9. Moyer AM, Skierka JM, Kotzer KE, Kluge ML, Black JL, Baudhuin LM. Clinical UGT1A1 Genetic Analysis in Pediatric Patients: Experience of a Reference Laboratory. Mol Diagn Ther. 2017;21:327-35.
10. Mitchell E, Ranganathan S, McKiernan P, et al. Hepatic parenchymal injury in Crigler-Najjar type I. J Pediatr Gastroenterol Nutr. 2018;66:588-94.
11. Fata CR, Gillis LA, Pacheco MC. Liver fibrosis associated with Crigler–Najjar syndrome in a compound heterozygote: A case report. Pediatr Dev Pathol. 2017;20:522-5.
12. Sun L, Li M, Zhang L, et al. Differences in UGT1A1 gene mutations and pathological liver changes between Chinese patients with Gilbert syndrome and Crigler-Najjar syndrome type II. Medicine. 2017;96:e8620.
13. Barış Z, Özçay F, Usta Y, Özgün G. Liver cirrhosis in a patient with Crigler Najjar syndrome. Fetal Pediatr Pathol. 2018;37:301-6.