

Case Report

Liver Transplantation in a Child with Crigler-Najjar Syndrome Type I: A Case Report

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ABSTRACT

Background: Crigler-Najjar syndrome is a rare autosomal recessive genetic disorder with incidence rate of one per a million live births. This syndrome often causes kernicterus and permanent damage to the nervous system due to high bilirubin level. We hereby present a child with Crigler-Najjar syndrome type I (CNS-I). **Case description:** The patient was an 18-month-old male infant referred to Taleghani Hospital in Gorgan due to jaundice at the first week of birth. CNS-I was confirmed by detecting high level of non-conjugated bilirubin. The patient was the second child of a consanguineous marriage (between cousins). The first child of the family was aborted in the first pregnancy due to infection. The patient underwent liver transplantation at age of six months. The patient was hospitalized several times due to fever and rectorrhagia following the liver transplantation, and eventually died of lymphoproliferative disorder. **Conclusions:** Early diagnosis at birth and therapeutic interventions including liver transplantation in the early months after birth could prevent the most common and dangerous complication of the disease, kernicterus. Moreover, genetic counseling should be provided for consanguineous couples.

KEYWORDS: Crigler -Najjar Syndrome, Hyperbilirubinemia , Liver transplant, Newborn

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INTRODUCTION

Crigler-Najjar syndrome (CNS) is an uncommon genetic disorder caused by a mutation in the UDP-glucuronosyltransferase gene located on chromosome 2q37, which is responsible for bilirubin removal. CNS type 1 (CNS-I) is the most severe hereditary condition of non-conjugated hyperbilirubinemia, which was first diagnosed by Crigler and Najjar. This autosomal recessive syndrome affects one per million live births. The most significant clinical symptom of CNS-I is severe jaundice. Serum concentration of bilirubin (non-conjugated) in patients with CNS-I is usually higher than 20 mg/dL, but can increase up to 30-50 mg/dL. There is currently no simple clinical test to confirm the diagnosis. DNA analysis can be very helpful in establishing the correct diagnosis. Patients with CNS-I are at risk of developing kernicterus and should immediately receive daily phototherapy during infancy. This condition is caused by a mutation in the UDP-glucuronosyltransferase gene located on chromosome 2q37, which is responsible for bilirubin removal [1]. This is

accompanied with absence of bilirubin conjugation with glucuronic acid that may lead to lack of bilirubin excretion from gallbladder, deposition of bilirubin in tissues, and brain damage [2]. Patients may suffer from mental retardation, seizure, cognitive impairment, sixth nerve palsy, ataxia and spasm. In addition, neurophysiological changes may be detected due to high bilirubin levels [3].

CASE PRESENTATION

The patient was an 18-month-old male infant (weighting 11 Kg) diagnosed with CNS-I who was referred to the hospital in the first week after birth with a chief complaint of jaundice. The patient was the second child of the family, born by cesarean section at 36th week of pregnancy. The first child of the family died due to an infection. Parents were related (cousins). There was no family history of heart disease, hypertension, diabetes or any other diseases. Definitive diagnosis was made by detection of persistent unconjugated hyperbilirubinemia. The patient was assessed for hemolysis, hypothyroidism,

infection, and all other common causes of jaundice. After ruling out other etiologies of indirect hyperbilirubinemia and based on family history and laboratory findings, diagnosis of CNS-I was made for the patient. The patient received phototherapy at home until 6 months of age. After performing liver

transplantation (LTx) at a treatment center (December 2014, Shiraz), the patient received tacrolimus, prednisolone and cotrimoxazole. The patient had elevated liver enzymes after 8 months of follow-up (Table 1).

Table 1. Post-transplantation laboratory findings

Tests	Detected level	Normal range
Gamma glutamyl transferase (GGT)	104.5 (high)	Normal: 7 – 32 U/L
Direct Bil	0.21 mg/dl	Up to 0.2mg/dl
Total Bil	1.09 mg/dl	0.2- 1.2 mg/dl
S.G.O.T (AST)	42.7 U/L (high)	Up to 37 U/L
S.G.P.T: (ALT)	49.2 U/L (high)	Up to 41 U/L

No pathological finding was reported in the renal and kidney ultrasound. Due to the increased level of liver enzymes, the patient was hospitalized for three days and received mycophenolate mofetil (CellCept). The patient was admitted to the hospital again three months later due to dyspnea. Since the symptoms were not relieved, the patient was referred to the transplant center. Administration of CellCept was stopped, and tacrolimus and prednisolone were prescribed. During the therapy, the patient developed rectorrhagia due to cow's milk protein sensitivity. Although rectal bleeding was controlled after removing dairy products from diet, blood reappeared in stool after a while. Due to suspected nosocomial infection, viral infection, septicemia and possibly gastroenteritis and cholangitis during the last time of hospitalization, the patient received metronidazole, cefixime and nystatin oral drops and symptomatic treatment with acetaminophen, salbutamol and packed cell. The patient died at age of 18 months due to post-transplant infection.

DISCUSSION

The patient was an 18-month-old child with CNS-I who died within a year due to post-LTx infection. CNS is a rare autosomal recessive heredity disorder, which is identified by elevated level of non-conjugated and non-hemolytic bilirubin caused by bilirubin UDP-glucuronosyltransferase 1 (B-UGT) enzyme

deficiency. Our case was diagnosed with CNS-I, which is far more severe than type 2 and requires treatment. In 1952, Crigler and Najjar described seven infants with congenital familial non-hemolytic jaundice who developed severe unconjugated hyperbilirubinemia shortly after birth and died from kernicterus within months. In study of Wang et al., all patients with CNS-I had increased level of non-conjugated bilirubin. Patients who do not receive timely treatment may develop kernicterus or die from encephalopathy. CNS is commonly seen in children from consanguineous marriages. In patients with CNS-I, UGT1A1 mutations are always accompanied with bilirubin UDPGT deficiency [4]. Similar to our study, in study of Tu et al., phototherapy was considered as an effective factor in the indirect control of hyperbilirubinemia in newborns. Moreover, determination of surface-to-weight ratio was emphasized for more therapeutic efficacy and estimating the time required for treatment. The child was treated with phototherapy until the age of 6 months. Recently, LTx has been effectively used for improving patients' quality of life for a medium-term period. Determining the suitable time for LTx is difficult, since the incidence of bilirubin encephalopathy is unpredictable.

In study of Tu et al., the patient received LTx five days after kernicterus [5]. Orthotopic liver transplantation is performed in patients without neurological complications, which

requires prolonged immune suppression. Due to better understanding of the pathophysiology of the disease and advances in phototherapy technology, patients with CNS-I can survive until adolescence and even adulthood [6]. However, our case could not survive despite treatment with phototherapy and LTx.

Therapeutic interventions including phototherapy, heme oxygenase-1 (HO-1) inhibitors and blood exchange can delay brain damage in patients with CNS-I. Nevertheless, LTx is the only definitive treatment for this syndrome, which should be performed before the onset of kernicterus [7]. In our case, the early phototherapy prevented the development of kernicterus. In study of Knudsen et al., a 7-day-old girl with CNS-I and 420 $\mu\text{mol/L}$ conjugated bilirubin level received phototherapy at home until the age of 14 years. Liver transplant was performed when her total bilirubin level was lowered to 250-300 $\mu\text{mol/L}$. The patient had no symptom of chronic encephalopathy caused by hyperbilirubinemia [8]. In the present study, the life span of patient was short due to the complications of immunosuppressive drugs. In study of Smerud et al., a 14-day-old newborn with history of apnea, retrocollis/opisthotonos and jaundice received triple phototherapy and blood transfusion from the second day of birth. However, chronic corneal infection occurred because of the delay in referral. This highlights the importance of early follow-up by the healthcare system for prevention of such cases [9]. Although our case had no brain complication, he developed complications due to late follow-up after the LTx and eventually died of infection.

CONCLUSION

Despite the early LTx, our case died due to suppressed immune system and widespread post-transplant infection. Considering the high frequency of consanguineous marriages in this region, it is essential to raise awareness of individuals and provide genetic counseling to prevent genetic diseases. Although LTx is the definitive treatment of this disease, risk of immunosuppression and post-LTx complications may influence the timing of this treatment plan. In fact, delayed LTx may be recommended in some instances.

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REFERENCES

1. Yan Li, Yu-jin Qu, Xue-mei Zhong, Yan-yan Cao, Li-min Jin, Jin-li Bai etc. Two unrelated patients with rare Crigler-Najjar syndrome type I: two novel mutations and a patient with loss of heterozygosity of UGT1A1 gene. *Journal of Zhejiang University. Science. B.* 2014; 15(5): 474-481.
2. Nadeali Z, Karimi A, Vallian-Borujeni S. Analysis of Genetic Variation of rs4148326 Marker Located in UGT1A1 Gene Region: An Informative Marker for Molecular Diagnosis of Crigler-Najjar Syndrome. *Journal of Isfahan Medical School.* 2014; 31(260): 1821-1828 [Article in Persian].
3. Bayram E, Öztürk Y, Hız S, Topçu Y, Kılıç M, Zeytinlu M. Neurophysiological follow-up of two siblings with Crigler-Najjar syndrome type I and review of literature. *The Turkish journal of pediatrics.* 2013;55(3):349-53.
4. Wang J, Fang LJ, Li L, Wang JS, Chen C. A new frame-shifting mutation of UGT1A1 gene causes type I Crigler-Najjar syndrome. *Chinese medical journal.* 2011; 124(23):4109-11.
5. Tu ZH, Shang DS, Jiang JC, Zhang W, Zhang M, Wang WL, et al. Liver transplantation in Crigler-Najjar syndrome type I disease. *Hepatobiliary & Pancreatic Diseases International.* 2012; 11(5):545-8.
6. Rela M, Muiesan P, Vilca-Melendez H, Dhawan A, Baker A, Mieli-Vergani G, et al. Auxiliary partial orthotopic liver transplantation for Crigler-Najjar syndrome type I. *Annals of surgery.* 1999; 229(4):565-9.
7. Tabarki B, Khalifa M, Yacoub M, Tlili K, Essoussi AS. *Pediatr Neurol. Cerebellar symptoms heralding bilirubin encephalopathy in Crigler-Najjar syndrome. Pediatric neurology.* 2002; 27(3):234-6.

8. Knudsen K, Ebbesen F, Andreasen AH. Crigler-Najjar's syndrome is a rare cause of perinatal hyperbilirubinaemia. *Ugeskrift for læger*. 2013; 14; 175(42):2492-3.

9. Smerud OJ, Solevåg AL, Hansen TW, Grønn M. A 14-day-old boy with jaundice and apnoea. *Tidsskr Nor Laegeforen*. 2015; 15; 135(23-24):2167-70 [Article in Norwegian].