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Case Report

Liver Transplantation in a Patient with Crigler-Najjar Syndrome Type 1: A Case Report of Two Cases

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ABSTRACT

Crigler Najjar syndrome(CNS); is a disease in which the diphosphate glucuronosyltransferase (bilirubin-UGT) enzyme function, which plays a role in the glucuronidation of bilirubin, is deficient as a result of mutation in the uridine 5'-diphosphate-glucuronosyltransferase 1A1 (UGT1A1) gene.1 As a result, non-hemolytic unconjugated hyperbilirubinemia is seen. Orthotopic liver transplantation (OLT) is seen as a curative treatment option in Crigler Najjar syndrome type 1 (CNS1). In this case report, we present our patients who were 11 months old and 8 years old with a diagnosis of CNS1, whose bilirubin levels were controlled by preoperative daily phototherapy and plasmapheresis, and who had OLT from their parents to two siblings. We wanted to show the importance of a close follow-up and multidisciplinary treatment approach in the early period before OLT in CNS1 patients and thus the benefit to the patient's prognosis in the postoperative period.

In CNS; As a result of the mutation in the UGT1A1 gene, it progresses with abnormal glucuronidation of bilirubin and as a result, non-hemolytic unconjugated hyperbilirubinemia. If the enzyme deficiency is complete it is classified as CNS1 and if it is part it is classified as Crigler Najjar syndrome type 2. No histopathological features are observed in diagnostic liver biopsy [1]. Enzyme function and UGT1A1 mutation can be used for diagnosis [2].

CNS is a very rare disease and its incidence is estimated at 1/1.000.000 births [3]. Neurological damage may occur due to bilirubin accumulation in the central nervous system in untreated or delayed treatment. Along with daily phototherapy, plasmapheresis can be used in the preoperative period to reduce the bilirubin level, prevent its accumulation and prevent this damage. The plasmapheresis filtering method, filters the high level of bilirubin bound to albumin in the plasma and gives the donor plasma to the patient.3 However, OLT is seen as a curative treatment option in CNS1 patients [2].

If we look at the prognosis in CNS patients, the prognosis in CNS1 patients is poor. CNS1 patients who do not receive treatment have high bilirubin levels, resulting in kernicterus and brain damage. OLT is seen as a curative option in these patients, but patients who cannot be transplanted can live a near-normal social life with phototherapy and plasmapheresis treatments [4].

In this case report, we present our patients who were 11 months old and 8 years old with a diagnosis of CNS1, whose bilirubin levels were controlled by preoperative daily phototherapy and plasmapheresis, and who had OLT from their parents to two siblings.

Case Reports

Case One

Ethics committee approval and written consent from the patient's relatives were obtained for both patients.

An 8-year-old child is admitted to the hospital with the complaint of jaundice 1 week after her birth. CNS1 is considered in the patient whose indirect bilirubin level was found to be high (18-25 mg/dL) in laboratory tests. She has been receiving phototherapy treatment for 10 hours a day since her birth. There was no response to the phenobarbital treatment (5 mg/kg) administered in another center. CNS1 diagnosis was made as a result of genetic testing.

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She was hospitalized for OLT. Plasmapheresis treatment was initiated to prevent central nervous system damage and kernicterus development due to high bilirubin levels. The liver donor was the patient's mother. No findings were found in the neurological examination and the intelligence test was evaluated as normal. No additional disease was detected in the controls. CHILD class B and PELD scores were calculated as 4.7. Central vein catheterization was applied to the patient one day before the operation. The patient was taken to the operating room on the day of surgery, and electrocardiography, non-invasive blood pressure, and pulse oximetry monitoring were performed. Fluid therapy was started from the central venous catheter. Anesthesia induction was achieved with 2 mg/kg of propofol, and 1 mg/kg of rocuronium was used as a muscle relaxant. She was intubated with direct laryngoscopy without complication. Bilateral lung sounds were evaluated as equal. Remifentanil 0.05 µg/kg/min and rocuronium 0.3 mg/kg/h were used as IV agents for anesthesia maintenance. Sevoflurane was used as an inhaler. Tidal volume was set to 6 mL/kg, PEEP: 4, respiratory rate was set to 14 in mechanical ventilator, and end-tidal CO2 was monitored. Left radial artery catheterization was provided. Arterial blood pressure, central venous pressure, and body temperature were monitored. Catheterization was provided with Pulse Contour Cardiac Output (PiCCO) and monitored. A 585 g graft was taken from her mother. The patient's vital signs, arterial blood gas parameters, and PiCCO values remained stable throughout the operation. 1500 mL of crystalloid liquid, 2000 mL of liquid containing 5% albumin, and 290 mL of erythrocyte suspension were administered. The anhepatic phase lasted 65 minutes.

Case Two

An 11-month-old child is admitted to the hospital with the complaint of jaundice 1 week after her birth. CNS1 is considered in a patient with a high indirect bilirubin level (25-35 mg/dL) in laboratory tests. She has been receiving phototherapy treatment 12 hours a day since her birth. There was no response to the phenobarbital treatment (5 mg/kg) administered in another center. CNS1 diagnosis was made as a result of genetic testing.

She was hospitalized for OLT. Plasmapheresis treatment was initiated to prevent central nervous system damage and kernicterus development due to high bilirubin levels. The liver donor was the patient's father. No findings were found in the neurological examination and the intelligence test was evaluated as normal. No additional disease was detected in the examinations and examinations. CHILD class B and PELD scores were calculated as 10. Central vein catheterization was applied to the patient one day before the operation. The patient was taken to the operating room, and anesthesia procedures were performed as in the previous case. 190 g graft was taken from her father. The patient's vital signs, arterial blood gas parameters, and PiCCO values remained stable throughout the operation. 1000 mL of crystalloid liquid, 1600 mL of 5% albumin-containing liquid, and 530 mL of erythrocyte suspension were administered. The anhepatic phase lasted 75 minutes.

The neohepatic phase was completed uneventfully. Both patients were recucarized with sugammadex 2 mg/kg. They were extubated. Patients with stable vital signs were transferred to the intensive care unit (ICU). The patients who were followed up in the ICU for one night were transferred to the service.

Discussion

CNS can be called congenital familial non-hemolytic jaundice. Two subtypes have been identified. While there is no diphosphate glucuronosyltransferase enzyme activity in CNS1 patients, it has partial activity in CNS2 patients.1 Therefore, the disease is seen much more severely in CNS1. And it can lead to kernicterus.

Many treatment options such as phototherapy, plasmapheresis, orlistat, phenobarbital, gene therapy are used in CNS1 patients. However, only OLT emerges as a curative treatment option [4].

Phototherapy provides a rapid and effective decrease in bilirubin levels in these patients. Thus, late complications and bilirubin accumulation can be prevented [5].

Orlistat is a lipase inhibitor and is often used in combination with calcium phosphate. It is assumed that it captures the intestinal indirect bilirubin and ensures its excretion together with the stool [6]. We did not use orlistat in our patients.

Phenobarbital induces and enhances the UGT enzyme, thereby increasing bilirubin conjugation. However, this drug is not effective due to the enzyme deficiency in CNS1 [4].

Plasmapheresis is seen as the most effective procedure in reducing unconjugated bilirubin levels. The process separates the plasma from the patient's blood and exchanges it with the donor plasma. During this process, unconjugated bilirubin, which is tightly bound to albumin, is also cleared together with the plasma [4].

There is no clear study that anesthetic drugs bind to protein and increase free bilirubin as a result. It is known that etomidate is 75 % protein bound. Propofol, on the other hand, increases the fatty acid components, leading to the separation of bilirubin from albumin and an increase in free bilirubin [7].

Schröder H. et. al. in their study; prepared 13 patients with CNS for OLT by applying preoperative daily phototherapy and phenobarbital therapy. Preoperative signs of central nervous system damage were present in 3 patients [8]. We prepared our patients for the operation by applying plasmapheresis treatment in addition to daily phototherapy. In this way, we reduced the rate of preoperative neurological damage and postoperative complications.

In a case presented by Zhen-Hua Tu et al.; the 18-month-old patient received daily phototherapy for up to 6

months with the diagnosis of CNS1 and was discontinued at the first hospital where this treatment was thought to be ineffective. Phenobarbital 15 mg/day treatment was started. In the 18th month, the patient was followed up by Zhen-Hua Tu et al. kernicterus was detected, and there was lethargy, hypertonia, and athetonia. The symptoms of the patient who underwent OLT regressed [9].

In these cases, we present our patients who underwent OLT after reducing bilirubin levels with preoperative phototherapy and plasmapheresis to two siblings diagnosed with CNS1. Both of our patients had been receiving daily phototherapy since birth. In this way, the development of kernicterus and neurological damage was prevented. After hospitalization, an effective bilirubin reduction (Table 1) was achieved with plasmapheresis treatment. Thus, we have provided the most optimal conditions for OLT.

Table 1- Unconjugated bilirubin values after plasmapheresis and OLT.

	Preoperative Unconjugated Bilirubin	**Unconjugated Bilirubin After Plasmapheresis**	**Unconjugated Bilirubin After OLT**
CASE 1	28 mg/dL	12 mg/dL	4 mg/dL
CASE 2	24 mg/dL	10 mg/dL	2 mg/dL

Conclusion

In CNS1 patients, good preoperative preparation, optimization, and conservative procedures, as well as correct anesthesia care with a large number of disciplines, are very important before OLT.

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