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Intrathecal baclofen therapy after liver transplant in a patient with Crigler-Najjar syndrome: a case report

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Abstract

Crigler-Najjar syndrome (CNS) is described as severe infantile, nonhemolytic, unconjugated hyperbilirubinemia, and is divided into Type I and Type II according to the patient's response to phenobarbital treatment. Type I CNS patients usually require liver transplant. These patients often suffer from spasticity and dystonia, both of which can be treated with intrathecal baclofen therapy (ITB). We present the case of a patient with CNS Type I who underwent a liver transplant followed years later by ITB therapy. To the authors' knowledge, this is the first report of a patient with CNS being treated for dystonia with an intrathecal baclofen pump. Despite his complicated history, this patient has remained medically stable following both interventions.

Introduction

Crigler-Najjar syndrome (CNS) has been defined for over 60 years as severe infantile, nonhemolytic, unconjugated hyperbilirubinemia [1] with the potential complications of central deafness, oculomotor palsy, ataxia, choreoathetosis, mental retardation, spasticity, and dystonia.[2] The disease is inherited by an autosomal recessive trait corresponding to glucuronyl transferase deficiency, the hepatic enzyme responsible for conjugating bilirubin for excretion. The frequency of CNS has been estimated at 0.6 per million.[3] Type II CNS patients exhibit decreased enzyme activity and hence a positive response to phenobarbital therapy, whereas Type I patients have complete absence of enzyme activity, do not respond to phenobarbital therapy, and thus often require liver transplantation.[3]

CNS patients sometimes suffer from spasticity and dystonia. One option for treating both of these conditions is the aminobutyric acid receptor agonist, baclofen, which can be administered both intraventricularly and intrathecally. However, to the authors' knowledge, this is the first report of a patient with CNS being treated for dystonia with an intrathecal baclofen pump. Despite his complicated history, this patient has remained medically stable for eleven years following liver transplant and placement of an intrathecal baclofen pump.

Case Report

This 22-year-old male was born with CNS Type I. During his first six years of life, treatment included 18–20 hours/day of treatment with phototherapy and a therapeutic dosage

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of phenobarbital (between 30–60 mg/day as the patient grew). Over these six years his average bilirubin level was 15 mg/dL, and he developed kernicterus manifested as spastic dystonia, which was controlled with 1–2mg/day of Ativan. By 6.5 years, it was clear that his bilirubin levels could not be maintained with phototherapy, as his skin was too thickened. Additionally, the patient became encephalopathic as his bilirubin approached 20 mg/dL.

The patient was evaluated for a liver transplant. At age 6 years 6 months, he received an auxiliary liver transplant, which was subsequently rejected. At age 7 years 10 months, the patient underwent a classic cadaveric orthotopic liver transplant. Immediately after surgery, he went into severe Ativan withdrawal requiring 70 mg/day by IV, which was tapered over 6–8 weeks to a minimum of 10mg/day. His physicians hypothesized that the glucuronyl transferase deficiency also affected Ativan metabolism, and therefore the effective pre-transplant dose was much higher than what was actually administered. Despite this complication, the transplant was successful, and resulted in complete resolution of his encephalopathy. The patient was also administered 2.5mg of Tacrolimus twice daily as an antirejection medication.

However, the patient continued to be limited by intense dystonic contractures and spastic paraparesis. This was treated with Ativan 10–20 mg/day, which had the undesired side effect of lethargy. Artane, Sinemet, and a variety of benzodiazepines in addition to Ativan (Valium, Klonopin, Xanax, Librium, and multiple combinations) were trialed as a potential treatment for dystonia, all with limited success. Oral baclofen was also tested to the point of excess sedation. Intrathecal baclofen was originally not an optimistic option; it was thought that his disease symptoms would not respond to the medication, as he was mostly unresponsive to oral baclofen. Notwithstanding, at age 11 years 2 months he underwent a lumbar puncture for a test dose of intrathecal baclofen, to which he responded dramatically. Two months later (almost four years after his successful liver transplant), an intrathecal baclofen pump was implanted subfascially with no noted complications involving the pump. As with any individual who has had multiple abdominal procedures, this patient was at an increased risk for wound infection, delayed wound healing, or even capsular migration. Fortunately, none of these occurred. After pump implantation, intermittent bolus dosing with dose escalation was initiated to determine the optimal daily amount of baclofen. At baclofen doses over 1050mcg/day, sleep apnea and dysphagia were observed. However, both complications resolved immediately upon reduction of the baclofen dose. Observed upon pump implantation were improvement in ease of activities of daily living, less spasticity, more relaxed tone, increased toleration of wheel chair with significant decrease in posturing, and some improvement in speech. His Ativan dosage was dropped to 5 mg/day after pump implantation. At age 15, the patient underwent posterior spinal fusion in attempt to stabilize his progressive kyphosis and scoliosis.

To date, the patient has had continued and definite, albeit slow, improvement in the ability to use his extremities. Before implantation of the baclofen pump, he was severely spastic, his arms drawn in with elbows flexed and fists in his face. With improvement of this spasticity, which the authors believe to be probably predominantly due to the ITB treatment, he has been able to concentrate on improving his grasp and semi-purposeful movement of his muscles. As the baclofen allows him to be more relaxed, he can concentrate on opening and closing his fists such that he currently has the ability to use a grasp or pressure switch. In addition, he is just now beginning to develop enough coordination to use a foot peddler to gain some degree of functional activity of his legs.

The patient's baclofen pump was replaced on January 1 of 2008, slightly over six years after the original pump was placed. The patient was last seen on January 2, 2013, and his aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (which are

typically used to check for liver damage) were within normal limits (16 U/L and 20 U/L, respectively). His current baclofen dosage is a basal rate of 30mcg/hour with a 99mcg bolus twice daily, for a total of 890mcg/day.

Discussion

CNS was originally described in 1952 by John F. Crigler and Victor Najjar as severe infantile, nonhemolytic, unconjugated hyperbilirubinemia in six inbred individuals from Maryland. Spasticity, opisthotonus, athetosis, and death before 6 months of age were observed in all but one of the six patients, and the sixth died at 15 years of age when kernicterus developed.[1] CNS is inherited by an autosomal recessive trait corresponding to glucuronyl transferase deficiency, the hepatic enzyme responsible for conjugating bilirubin for excretion.[3]

CNS has been further divided into Type I, the phenobarbital-unresponsive, more severe form, and Type II, the phenobarbital-responsive, less severe form. Patients with Type II have been shown to demonstrate a 25% decrease in serum bilirubin levels after 5 days of treatment with phenobarbital, whereas Type I patients exhibit little to no response to phenobarbital therapy. Type I, which is seen in this case, involves complete glucuronyl transferase deficiency, while Type II patients show decreased, but not absent, enzyme activity.[3] Kernicterus is a potential complication in both disease types, and severe cases of bilirubin encephalopathy can lead to central deafness, oculomotor palsy, ataxia, choreoathetosis, mental retardation, seizures, spasticity, and dystonia.[2] The patient presented in this study was significantly limited by his spasticity and dystonia in particular.

Type I CNS patients require 10–12 hours/day of phototherapy until they receive a liver transplant. Phototherapy alone has been noted to be more effective earlier in life, but becomes less effective in the post-puberty years.[4] The first successful orthotopic liver transplantation in a patient with CNS Type I disease was reported in 1986 by Kaufman et al. [5] This technique has since been recommended for patients whose bilirubin levels can no longer be maintained by phototherapy alone. Liver transplantation should be performed before bilirubin neurotoxicity is detected.[6]

Some CNS patients, like the one we present here, suffer from spasticity and dystonia. Baclofen is a gamma-aminobutyric acid receptor agonist used to treat these symptoms in many diseases. In severely spastic or dystonic patients, ITB pumps are often placed in order to continuously deliver the drug to the central nervous system. ITB for the treatment of dystonia was first reported in 1991, and has since been recommended as a safe and effective treatment for dystonia.[7,8] In addition, Ford et al suggest that ITB as a treatment for dystonia is more effective in patients who also have spasticity,[9] which is another common symptom in CNS. ITB has been shown to be effective in treating secondary dystonia in other disorders such as cerebral palsy, [10] chromosome 18p deletion, [11] Wilson's disease, Huntington's disease, pantothenate kinase-associated neurodegeneration (PKAN), anoxia, traumatic brain injury (TBI), mitochondrial disorders, glutaric aciduria, thrombosis, and holoprosencephaly.[12] Intraventricular baclofen has been used to treat cerebral palsy, methylmalonic aciduria, TBI, anoxia, PKAN, and striatal lesions.[13,14]

It is important to note that the improvements noted in this patient cannot be attributed to either liver transplant or ITB alone, as it is likely that his progress is a result of both interventions. Although the patient regained certain functional abilities only after starting ITB, it is also possible that natural neurologic recovery or the development of compensatory mechanisms after liver transplant (and therefore after the static insult of high bilirubin in the brain had diminished) also contributed to his long-term progress.

Conclusion

This case demonstrates the success in one patient with CNS of liver transplantation accompanied by subsequent baclofen pump implantation. This patient responded well to both procedures, experienced minimal complications, and has achieved greater motor ability in response to both therapies. In addition, he has remained stable for eleven years following liver transplant and on ITB. To the authors' knowledge, baclofen has not been reported as a treatment for spasticity and dystonia in patients with CNS. Due to this paucity of literature, it is difficult to compare outcomes of this treatment with any other patients. This treatment option might also be considered in other hepatic-based metabolic diseases in which liver transplantation is implicated and severe spasticity or dystonia is a limiting factor in the patient's quality of life.

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