Management of Crigler-Najjar syndrome

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Abstract

Crigler-Najjar syndrome is a rare autosomal recessive inherited non-hemolytic unconjugated hyperbilirubinemia caused by UDP-glucuronosyltransferase deficiency. There are two forms of this disorder. Type 1 disease is associated with severe jaundice and neurologic impairment due to bilirubin encephalopathy that can result in permanent neurologic sequelae. Type 2 disease is associated with a lower serum bilirubin concentration and affected patients survive into adulthood without neurologic impairment. Currently, liver transplantation is the only available therapeutic method for these patients. Developing new curative approaches is a clinical need.

Keywords: Crigler-Najjar syndrome, diagnosis, therapy

Introduction

Mutations in the common or in the bilirubin-specific regions of the bilirubin-uridine diphosphate glucuronosyltransferase (UGT1A1) gene, affecting its expression and/or activity, lead to different forms of unconjugated hyperbilirubinemia: Gilbert syndrome, Crigler–Najjar syndrome type 1, Crigler–Najjar syndrome type 2.

Gilbert syndrome is the most benign form of hereditary unconjugated hyperbilirubinemia and these patients carry a normal life. They present total serum bilirubin levels rarely exceeding 60 µmol/L (4 mg/dL) [1]. Other liver tests and bile acid tests are normal. Although total serum bilirubin levels may rise during starvation or upon hepatic complications, Gilbert syndrome patients have almost no risk of developing brain damage. The disorder affects approximately 3–7% of individuals in the general population [1].

Crigler-Najjar syndrome type 1 was described by Crigler and Najjar in 1952 in six infants in three families [2]. Patients with Crigler-Najjar syndrome type 1 have total serum bilirubin levels exceeding 20 mg/dL (340 µmol/L) and can increase up to 50 mg/dL (850 µmol/L). This is the most severe form of the disease since patients completely lack UGT1A1 enzyme activity. Bile acid test in these patients showed that bile is almost completely composed by unconjugated bilirubin with only traces of mono-glucuronide bilirubin. Untreated patients develop severe neurological damage and are at constant risk of kernicterus.

Crigler-Najjar syndrome type 2 patients have total serum bilirubin levels in the range of 3.5–20 mg/dL (60–340 µmol/L). It is also known as Arias syndrome and shows a better outcome [3]. In fact, these patients have a residual UGT1A1 enzymatic activity (less that 10%), which is sufficient to maintain unconjugated bilirubin levels below the risk of developing serious neurological damage. UGT1A1 enzymatic levels can be increased by treatment with phenobarbital, which stimulates UGT1A1 gene transcription [4].

Crigler-Najjar syndrome affects 0.6 to 1 in 1 million newborns around the world [5,6].

Etiology

Deletion, alterations in intron splice donor and receptor sites, missense mutation, exon skipping, insertion, or the formation of a stop codon within the UGT1A1 gene are the main mutations in type I Crigler-Najjar syndrome, which

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leads to complete deficiency of enzyme UGT [7,8]. On the other hand, type II Crigler-Najjar syndrome results from a point mutation in the UGT1A1 gene resulting in decreased production of enzyme UGT [5,7].

The neurological outcome

Unconjugated bilirubinemia travels in the bloodstream bound to albumin and, in normal conditions, the amount of unbound unconjugated bilirubinemia is negligible (less than 0.1%) [1,9]. When unconjugated bilirubinemia levels exceed the albumin binding capacity, the fraction of unbound unconjugated bilirubinemia, also known as free bilirubin, increases and accumulates in lipophilic tissues such as the brain, causing neurological damage [1,10].

Milder and reversible forms of neurological disorder are characterized by bilirubin-induced neurological dysfunction, with hypotonia, lethargy and anorexia. In more severe cases patients develop moderate movement disorders such as abnormal gait, imbalance, impaired fine motor skills and ataxia due to the deposition of bilirubin in the basal ganglia and cerebellum.

The most severe, irreversible form is kernicterus. The term refers to the anatomic diagnosis made at autopsy, based on the pattern of brain staining and literally indicates ”yellow nuclei”. In fact, bilirubin deposition in the brain occurs mainly in basal ganglia, globus pallidus, hippocampus, subtalamic nucleus, horn of Ammon, cranial nerve nuclei, and the cerebellum [1,11]. Kernicterus is associated by choroathetoid cerebral palsy, high-frequency central neural hearing loss, palsy or vertical gaze and dental enamel hypoplasia .The untreated kernicterus has a poor prognosis and may lead to death.

Diagnosis

By means of an elaborate clinical evaluation, characteristic finding, detailed patient history and specialized testing, the diagnosis may be suspected in the first few days of life in newborns. Likely in Rh disease (isoimmunization), blood tests reveal abnormally high levels of unconjugated bilirubin in the absence of expanded levels of red blood cell degeneration (hemolysis). Further, a lack of bilirubin is established by urine analysis and no detectable bilirubin glucuronides is established by bile analysis.

The diagnosis of Crigler Najjar syndrome can be confirmed by a molecular genetic test.

Mutation in the UGT1 A1 gene, that are known to cause the disorder can be detected by molecular genetic testing, although it can be done only at specialized laboratories.

It is essential to identify Crigler-Najjar syndrome type I and type II. For Crigler Najjar syndrome type II and Gilbert Syndrome it is prescribed the administration of phenobarbital, a barbiturate which reduces blood bilirubin levels. Meanwhile, this prescription is not effective for those with syndrome type I. Hence, the failure to respond to this medication it is a critical indication for comprehend diagnosis purposes.

Treatment

There are two main categories of potential treatments: control bilirubin and its neurotoxic effects (phototherapy, plasmapheresis, pharmacological treatments) and restore UGT1A1 activity in hepatocytes (cell therapy and gene therapy).

Intensive phototherapy is a common treatment for Crigler-Najjar type I syndrome and is often part of the treatment of neonatal hyperbilirubinemia [7,12]. Compared to the conventional way, intensive phototherapy brings quicker and more effective responses [7,13]. It also contributes for shorter periods of treatment and lessen late complications. Older children and adults will encounter a decreased effect of such treatment because of thicker skin, increased skin pigmentation, and less body surface area to body mass [7,14].

Plasmapheresis is the most effective process to remove the excess unconjugated bilirubin from the blood during severe hyperbilirubinemia crisis. Plasmapheresis is a process for removing any unwanted substance from the blood. During plasmapheresis, blood is removed from the affected patient, and blood cells are separated from plasma. The plasma is then replaced with the donor plasma, and the blood transfused back into the affected patient. As bilirubin is tightly bound to albumin, removal of albumin during this process leads to a reduction of bilirubin in the blood.

Pharmacological treatment includes enzyme-inducing agents (phenobarbital), bilirubin-binding agents (calcium phosphate, orlistat), choleretics (ursodeoxycholic acid), heme-oxygenase inhibitors (Tin-protoporphyrin, Zinc-protoporphyrin).

When unconjugated bilirubin reaches toxic levels, the disease is managed with aggressive intravenous fluid hydration, administration of albumin, and possibly plasma exchange to avoid serious neurological consequences. Albumin infusion increases the bilirubin plasma-binding capacity capturing bilirubin excess and, thus, lowering the total body exchangeable unconjugated bilirubin fraction and preventing its movement and accumulation in extravascular sites. Its use is accepted in many clinical centers [1,15-17]. Ursodeoxycholic acid, lipid-rich food, calcium carbonate may be given to increase the intestinal flow or to trap bilirubin in the intestinal lumen, maximizing elimination of unconjugated bilirubin and derivatives with the feces [18]. However, those treatments present significant limitations and may have, in some cases, important risks and undesired side effects.

Therapies based on the transplantation of allogeneic hepatocytes or hepatocyte progenitor cells have the potential to cure inherited liver disorders. Transplantation of isolated allogenic hepatocytes has been attempted in Crigler-Najjar patients, however achieving only limited and transient benefit [1,18,19]. The poor levels of engraftment of transplanted cells and the lack of growth advantage of the transplanted cells resulted in a decline in cell function after 9–11 months, requiring liver transplantation. Similar results were also shown in a recent cell transplantation trial with mesenchymal stem cells [20]. Different approaches have been used in animal models to increase engraftment rate, ranging from partial hepatectomy, irradiation, CCl_4 treatment, to block of endogenous hepatocyte proliferation [21-23]. However, these treatments cannot be applied to patients and safer strategies need to be developed.

Consequently, hepatocyte transplantation in Crigler-Najjar patients is performed as a temporary therapeutic alternative approach or ”bridge” for patients waiting for whole organ transplantation [1].

Gene therapy by gene replacement consists in the addition of new genes to a patient’s cells to replace missing or malfunctioning ones. Recombinant adeno-associated virus (AAV) vectors is the most efficient approach for introducing genetic material into diseased liver cells. Is is potential therapies for Crigler-Najjar syndrome in the future [1].

Liver transplantation is the only therapeutic and definitive treatment method in Crigler-Najjar type 1. Two principal types of liver transplantation are used to treat patients with Crigler-Najjar syndrome type 1: orthotopic liver transplantation (OLT) and auxiliary partial orthotopic liver transplantation (APOLT). Post-transplant survival rates: 86–100% at 1 year, 81–95% at 5 years and 79–92% at 10 years.

In conclusion, the Crigler–Najjar syndrome is an ultra-rare recessive disorder of the liver. Type 1 disease is associated with severe jaundice and neurologic impairment due to bilirubin encephalopathy (also called kernicterus). Type 2 disease is associated with a lower serum bilirubin concentration and affected patients survive into adulthood without neurologic impairment. The development of gene therapy products containing the UGT1A1 gene will open new perspectives. The development of novel therapeutic approaches is a clinical need. Liver transplantation remains the only curative therapy for Crigler-Najjar syndrome type 1.

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