

# Management of Crigler-Najjar Syndrome type I

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## ABSTRACT

Crigler-Najjar Syndrome type I is a rare congenital disease with high mortality and morbidity rates due to brain complications. It has been treated by life-long phototherapy until the era of liver transplantation. Liver transplantation is currently the only curative treatment for this syndrome. Liver transplantation prevents the severe neurological complications that are the main cause of life-long disability in Crigler-Najjar Syndrome type I. The ideal age for transplantation is 3-5 years. Despite the advent of auxiliary transplantation we believe that orthotopic liver transplantation is the optimal treatment and the ideal method of liver transplantation for Crigler-Najjar Syndrome type I.

**Keywords:** Crigler-Najjar Syndrome type I, liver transplantation, orthotopic liver transplantation, auxiliary partial orthotopic liver transplantation.

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In 1952, Crigler and Najjar described 7 infants with congenital familial non-hemolytic jaundice who developed severe unconjugated hyper-bilirubinemia shortly after birth and died from kernicterus within months.<sup>1</sup> In 1969, Arias et al published observations describing a 2nd and more frequent type of less severe non-hemolytic hyperbilirubinemia.<sup>2</sup> To differentiate between the 2 diseases, the former is called Crigler-Najjar Syndrome type I (CNS-1), while the later is called Crigler-Najjar Syndrome type 2 (CNS-2) or Arias syndrome.<sup>2</sup> Crigler-Najjar Syndrome results from a mutation in one of the 5 exons of the gene coding for the enzyme Uridine DiPhosphate-Glucuronyl Transferase (UDP-GT) on human chromosome number 2 and 4.<sup>3,4</sup> This leads to an born error of bilirubin metabolism due to complete deficiency of UDP-GT in CNS-1, and partial deficiency of UDP-GT in CNS-2.<sup>4</sup> The affected infants have unconjugated hyperbilirubinemia from birth.<sup>1</sup> Crigler-Najjar

Syndrome occurs with an estimated frequency of around 0.6 per million newborn.<sup>4</sup> Approximately 170 cases of CNS have been reported in the literature so far,<sup>3</sup> approximately 76 cases were CNS-1.<sup>4</sup> Crigler-Najjar Syndrome type I is less frequent than CNS-2 with serum bilirubin values of untreated patients in excess of 350  $\mu\text{mol/L}$  and the bile containing not more than traces of bilirubin conjugates. Crigler-Najjar Syndrome type 2 is less severe than CNS-1 with serum bilirubin values usually not exceeding 350  $\mu\text{mol/L}$  and the bile contains bilirubin mono- and diglucuronides, but in low concentrations.<sup>4</sup> The serum bilirubin level in CNS-2 responds to phenobarbital treatment with a decrease of 30% or more while, CNS-1 does not show such a response to phenobarbital (see Table 1). This can be used as a test to differentiate between the 2 diseases. It has been accepted that CNS-1 represents an autosomal recessive inheritance. There is

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**Table 1** - Differences between CNS-1 and CNS-2.

| Variable                     | CNS-1                      | CNS-2                    |
|------------------------------|----------------------------|--------------------------|
| Inheritance mode             | Autosomal recessive        | Autosomal recessive      |
| UDP-GT level                 | Complete absence           | Partial Deficiency       |
| Frequency                    | Less than CNS-2            | More than CNS-1          |
| Severity                     | More than CNS-2            | Less than CNS-1          |
| Serum bilirubin              | More than 350 umol/L       | Less than 350 umol/L     |
| Bilirubin conjugates in bile | Trace                      | Low                      |
| Kernicterus                  |                            |                          |
| - Onset                      | - Early                    | - Late                   |
| - Severity                   | - More severe than CNS-2   | - Less severe than CNS-1 |
| Response to Phenobarbital    | No response (Negative)     | Good response (Positive) |
| Treatment                    | Phototherapy and later LTX | Phenobarbital            |

CNS 1=Crigler-Najjar Syndrome type 1, CNS-2=Crigler-Najjar Syndrome type 2, LTX=Liver Transplantation

considerable overlap of hepatic UDP-GT between CNS-2 and Gilbert's syndrome.<sup>6</sup> It was suggested that CNS-2 may represent homozygous Gilbert's syndrome,<sup>7,8</sup> but the inheritance mode is also autosomal recessive.<sup>3</sup> Crigler-Najjar Syndrome does not cause structural damage to the liver but causes severe and life-threatening extra-hepatic complications, mainly neurological.<sup>10</sup> Kernicterus is a serious complication of both CNS type 1 and 2 and describes the staining of the basal ganglia such as globus pallidus and subthalamic nuclei and cranial nerve nuclei.<sup>3</sup> In the most serious form, bilirubin encephalopathy leads to central deafness, oculomotor palsy, ataxic choreoathetosis, mental retardation, seizures, spasticity, and death.<sup>11</sup> There are less severe forms, which lead to ataxia, deafness and slurred speech. A sudden deterioration of gait, handwriting or speech can develop during periods of high serum bilirubin levels. This sometimes is reversible when adequate measures to decrease serum bilirubin are immediately taken. In patients with CNS, kernicterus may develop at any age and is not confined to the very young age group,<sup>3</sup> but actually the older child is

**Table 2** - Modalities of treatment for CNS-1.

1. Exchange blood transfusion/dialysis
2. Phototherapy
3. Gene therapy (experimental)
4. Hepatocyte transplantation (experimental)
5. Medications for example tin-portoporphyrin
6. Liver transplantation

at a higher risk for developing neurological deficits. The pre- and post-pubertal ages are in the greatest risk phases of developing kernicterus. It is mainly induced by infection. In this paper we will review CNS-1 and its management and we will try to answer 3 important questions in the management of this syndrome: 1. Do we need liver transplantation in the treatment of CNS-1? 2. Which age is ideal for the liver transplantation in CNS-1? 3. What type of liver transplantation should be carried out in CNS-1?

**Treatment of CNS-1.** Before the wide spread of phototherapy, CNS-1 was lethal with death from kernicterus between the age of one and 2 years.<sup>1,12</sup> Treatment of CNS-1 consists of exchange blood transfusion soon after birth followed by 10-12 hours of phototherapy per 24 hours.<sup>3</sup> Patients with CNS-1 need life-long phototherapy until liver transplantation is performed. Normally, CNS-2 can successfully be treated by phenobarbital, but uncontrolled patients may also need liver transplantation. The available modalities of treatment for CNS-1 are illustrated in Table 2.

**Exchange blood transfusion/peritoneal dialysis.** This is carried out soon after birth then followed by the phototherapy.<sup>3</sup> It is only practical after delivery and in severe acute case of unconjugated hyperbilirubinemia in which bilirubin levels must be reduced in a very short time.<sup>13</sup> Blood transfusion carries a lot of risks to the recipient, from blood reactions to blood born infections. It also cannot be used on a daily basis for treating CNS-1 patients.

**Phototherapy.** This treatment should be started soon after birth following the exchange blood transfusion. Despite a mean daily phototherapy of 12.4 +/- 0.8 hours, hyperbilirubinemia is partially treated.<sup>14</sup> Phototherapy will be needed life long on a 10-16 hour/day basis. This will have a direct effect on the quality of the life. The response to the phototherapy is decreasing with age leading to increased risk of kernicterus. This decrease in phototherapy effectiveness is probably due to of unfavorable body surface / weight ratio and decrease in the compliance,<sup>15</sup> in addition to the change in skin pigmentation and its thickness. Twenty six percent of the patients developed brain damage while they are on phototherapy.<sup>14</sup> The compliance to the phototherapy is very difficult especially for the patient's family unless they are educated and carefully instructed.

**Gene therapy.** As a disease model, CNS seems ideally suited for gene replacement and gene repair therapy. When it will be available, gene therapy will therefore be expected to cure the patient entirely. It is so far not possible to apply such treatment to patients with CNS-1. A similar genetic defect has been corrected in the Gunna rat, an experimental model of CNS-1, by retroviral gene transfer.<sup>16</sup>

**Hepatocyte transplantation.** Recently hepatocyte transplantation was reported in a child with

CNS-1 whereby normal donor hepatocytes were administered via the percutaneous, transhepatic intraportal route. During a follow-up of 136 days, phototherapy could be reduced from 12-8 hours while maintaining the serum bilirubin level below 250  $\mu\text{mol/L}$ . After hepatocytes transplantation, the bile contains bilirubin mono- and diglucuronides. Immuno-suppressive therapy consists of FK506 and prednisolone.<sup>17</sup> Encapsulated hepatocytes transplantation has also shown success in lowering serum bilirubin in a guinea rat.<sup>18</sup>

**Drug therapy.** Treatment with heme-oxygenase inhibitors such as tin-protoporphyrin or zinc-mesoporphyrin, may block bilirubin formation. This treatment helps to decrease the serum bilirubin temporarily and may shorten the daily duration of the phototherapy. However, tin-protoporphyrin treatment increases the photosensitivity of the skin. These agents can be used during sudden bilirubin elevation caused by inadvertent termination of the phototherapy or during inter current illness. The effectiveness of porphyrin treatment under these conditions remains unproven since in practice, several procedures are usually carried out at the same time.<sup>3</sup> Tin-protoporphyrin has been used in one CNS-1 patient with data suggesting decreased need for phototherapy.<sup>19</sup>

**Liver transplantation (LTX).** Liver transplantation currently is the only definitive therapy for CNS-1.<sup>15,20</sup> Liver transplantation can be living-related LTX or cadaveric LTX. Two types of LTX have been tried: orthotopic liver transplantation (OLT) and auxiliary orthotopic liver transplantation (AOLT). The first OLT for CNS-1 was reported by Wolf and Otto in 1980 and published in 1986 and their patient is currently alive and well.<sup>14,21</sup> Whittington and his colleagues reported the first auxiliary orthotopic LTX for CNS-1 in 1993. However, the results are not satisfactory and the patients still suffer from the pre-transplantation neurological complications.<sup>20</sup>

### **Results. Why do we need liver transplantation in CNS-1?**

There are several reasons for LTX treatment in CNS-1: 1. The other available modalities of treatment are less effective and temporary. 2. They are disturbing the normal quality of life. 3. Poor compliance to these types of treatments. 4. The risks of complications of these treatments. Gene therapy, hepatocyte transplantation, and tin-protoporphyrin treatment are still experimental. Liver transplantation will be necessary sooner or later;<sup>3</sup> Kernicterus should be avoided at all costs, it can precipitate without warning. Children with kernicterus should not be considered as LTX candidates due to its irreversibility, in some centers;<sup>3</sup> the available reported cases of CNS-1 that were treated by LTX at appropriate selection, have shown very good results;<sup>4</sup> LTX currently is the only

definitive and curative therapy for this disease.<sup>15,20</sup> So LTX is the treatment of choice for all patients with CNS-1.

**Which age is ideal for the liver transplantation in CNS-1?** The timing of LTX for this disease is a matter for debate. It is vital that the LTX should be performed before the neurological complications (major) development, since these are irreversible changes, and major neurological damages are contraindications for LTX.<sup>3</sup> In our view it is appropriate to undertake LTX for these children between the age of 3 and 5 years before they attend the school. This has the advantage of minimizing disruption to their education while reducing the difficulties in obtaining a suitable donor due to size matching. Older children have a higher risk of kernicterus and most of the reported cases of older than this age have variable degrees of neurological deficits.<sup>4</sup> Effects of phototherapy drastically decrease after this age with significant increase of neurological damage frequency. It also avoids the problems of poor compliance with advancing age.<sup>15</sup> The social acceptability and the quality of the phototherapy may influence the time point for transplantation in one direction or the other.

### **What type of liver transplantation in CNS-1 should be carried out?**

These types of LTX have been used in the treatment of CNS-1: OLT and APOLT. Orthotopic liver transplantation: In this case a total hepatectomy is performed and a liver or partial liver from a living or cadaveric donor is transplanted. Early cases proved the efficacy of this treatment for CNS-1: In a series of 6 patients treated by OLT Sokal et al demonstrated that OLT cures hyperbilirubinemia with an excellent survival prospect.<sup>14</sup> Recently, cases in Riyadh and in Hamburg confirmed that living donation from mother or father also cures the disease. The operative technique of OLT is well established and can be performed with very low mortality and morbidity rates in children with metabolic disease. Size matching is easier due to the availability of a larger space for whole liver or splitted liver after complete native liver hepatectomy. Auxiliary partial orthotopic liver transplantation: In the world registry of CNS-1 published in 1996 by Van der Veere et al, 18 (86%) patients out of 21 patients treated by LTX had OLT and 3 (14%) patients had APOLT.<sup>4</sup> The latter technique consists in the partial removal of the native (patients own) liver and the transplantation of part of a healthy liver in this position. The small amount of transplanted liver tissue is sufficient to correct the metabolic defect of CNS-1. The proposed advantage of APOLT is that it allows the native liver to be preserved to help in case of graft failure. Theoretically it also preserves the possibility for gene therapy if it develops to be successful in the future.<sup>10</sup> The first argument is not really valid as retransplantation will be required in case of graft failure in both OLT and APOLT.

Regarding the gene therapy, those patients who were transplanted by either OLT or APOLT should not need this type of treatment if they are cured by LTX. Auxiliary partial orthotopic liver transplantation is technically a more demanding procedure with higher rates of complications. To avoid a steal of portal blood to the native liver, resulting in atrophy and dysfunction of the graft, the portal vein of the native liver has to be banded. Also, diagnosis and management of rejection in APOLT is much more difficult than in OLT. In both OLT and APOLT, immuno-suppression should be used. Out of 11 patients with CNS-1 who have been reported to be treated by APOLT, only 6 patients reported to have good results.<sup>4,15,20</sup> These findings are questioning the value of APOLT for this indication.

In conclusion, CNS-1 is a rare congenital disease with high mortality and morbidity rates. It has to be treated immediately after the birth, to prevent the neurological complications, by exchange blood transfusion followed by photo therapy. Those patients should undergo LTX, which is the only available curative treatment for this disease. It is ideally performed at the age of 3-5 years. Orthotopic liver transplantation is currently the preferred type of LTX in the treatment of CNS-1.

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