Eur J Pediatr (2009) 168:427–429
DOI 10.1007/s00431-008-0763-5

ORIGINAL PAPER

Normal neurological outcome in two infants treated with exchange transfusions born to mothers with Crigler-Najjar Type 1 disorder

Simon Hannam · Paul Moriaty · Helen O'Reilly · John S. Craig · Michael A. Heneghan · Alastair Baker · Anil Dhawan

Received: 9 April 2008 / Accepted: 13 May 2008 / Published online: 13 June 2008

Abstract Patients with Crigler-Najjar Type 1 (CN-1) disorder have an unconjugated hyperbilirubinaemia due to the complete absence in activity of uridinediphosphate glucuronosyltransferase, a bilirubin-conjugating enzyme. In pregnant women with CN-1, the foetus is at high risk of being adversely affected by the bilirubin, as unconjugated bilirubin can cross the placenta and is potentially neurotoxic. We report the long-term outcomes of two infants born to women with CN-1. These infants had exchange transfusions soon after birth and have normal neurodevelopmental outcomes at 18 months and four years of age, respectively. We propose that this intervention might have improved the neurological outcome of these infants.

Keywords Jaundice · Kernicterus · Bilirubin · Unconjugated · Neurodevelopment

Abbreviations

CN-1	Crigler-Najjar Type 1
UDPGT	Uridinediphosphate glucuronosyltransferase
PCV	Packed cell volume
AABR	Automated auditory brainstem response
MRI	Magnetic resonance image

There are no conflicts of interest reported by any of the authors.
Funding was not required.

S. Hannam (✉) · H. O'Reilly · A. Baker · A. Dhawan
Department of Child Health, Kings College Hospital,
London SE5 9RS, UK
e-mail: simon.hannam@kcl.ac.uk

P. Moriaty · J. S. Craig
Regional Neonatal Unit, Royal Maternity Hospital,
Belfast BT12 6BB, UK

M. A. Heneghan
Institute of Liver Studies, Kings College Hospital,
London SE5 9RS, UK

Introduction

Crigler-Najjar Type 1 (CN-1) disorder is caused by the complete absence in activity of uridinediphosphate glucuronosyltransferase (UDPGT), a bilirubin-conjugating enzyme. Due to the high levels of unconjugated bilirubin present from the time of birth, there is a long-term risk of brain damage [8]. The management of pregnancy in women with CN-1 has been based on the concern that maternal levels of unconjugated bilirubin would be extremely toxic to the foetal brain. As a result, our advice given to pregnant women with CN-1 had been to terminate the pregnancy. We report the long-term outcome of two infants born to mothers with CN-1. These infants had exchange transfusions soon after birth and have normal neurodevelopmental follow-up at 18 months and four years of age, respectively.

Case reports

Case 1

A 26-year-old woman with CN-1 presented to her routine follow-up appointment in the hepatology clinic five weeks pregnant. She had presented at three days of age with an unconjugated bilirubin of 376 μmol/L and needed an exchange transfusion. Her parents were first cousins. Of note, she had a first cousin with CN-1 whose parents were also consanguineous. On the basis of this family history,

CN-1 was diagnosed after the exclusion of other causes of unconjugated hyperbilirubinaemia. She refused to have a liver biopsy. Since childhood, she had been treated with phototherapy, resulting in bilirubinaemias ranging between 400 and 500 μmol/L. She had also been treated with phenobarbitone and cholestyramine. Her development was normal and she attended a mainstream school. A liver transplant had been suggested, but she had declined this treatment option. She had had two terminations due to concern that the foetuses would have been severely affected by the high bilirubin levels.

The woman's serum bilirubin was 526 μmol/L when she presented in the antenatal clinic. She was, therefore, advised to increase her daily phototherapy from 11 to 14 hours. During the remainder of the pregnancy, her bilirubinaemia was between 200 and 380 μmol/L. Antenatal ultrasound scans were normal. There was no history of consanguinity. At 36 weeks, she presented with bleeding and spontaneous rupture of membranes. Labour was induced with prostin, but an emergency caesarean section was subsequently performed for oblique lie and foetal distress.

A male infant was delivered weighing 1.9 kg (0.4th–2nd percentile). His unconjugated bilirubin at birth was 323 μmol/L, which was well above the threshold for exchange transfusion. His mother's unconjugated bilirubin at the time of delivery was 317 μmol/L. The initial packed cell volume (PCV) was 46% (normal range: 40 to 60%). This suggested that the hyperbilirubinaemia was not the result of haemolysis. His albumin level was within the normal range and his arterial pH was always above 7.30. Phototherapy was commenced and phenobarbitone was given. He had a double-volume exchange transfusion via umbilical venous and peripheral arterial lines at 7 hours of age, which resulted in a rapid decline of his bilirubinaemia to 214 μmol/L by 10 hours of age. Phototherapy was continued for a further three days. He was clinically well on discharge at ten days of age, with a bilirubin level of 260 μmol/L. Prior to discharge, he had a normal automated auditory brainstem response (AABR). A magnetic resonance imaging (MRI) scan on the fifth day of life showed appropriate myelination for age, with T1 high signal in the globus pallidus bilaterally consistent with the deposition of bilirubin. He was closely monitored in the outpatient clinic. He walked at 14 months of age. There were concerns about his verbal skills, but by four years of age, his neurological examination was normal and his speech and language skills were within normal limits. A repeat MRI scan of his brain at three years of age was also normal.

Case 2

A 22-year-old woman with CN-1 presented in her first pregnancy. Her elder brother had CN-1 and she had been diagnosed with CN-1 in the neonatal period following a liver biopsy that had not demonstrated any glucuronyl transferase activity. She had had three auxiliary liver transplants, in 1993, 2001 and 2003, respectively. The most recent transplant had not been successful in controlling her bilirubin levels, resulting in unconjugated bilirubin levels of between 320 and 460 μmol/L. Unfortunately, she had found it difficult to comply with the advised regimen of 16 hours of phototherapy per day. During the first trimester of pregnancy, she had received fortnightly albumin infusions, which had not improved her degree of jaundice. Her bilirubinaemia varied in the pregnancy between 399 and 510 μmol/L.

She went into spontaneous labour at 37 weeks of gestation, and a male infant was born by vaginal delivery. His birth weight was 3.06 kg (50th centile). The cord unconjugated bilirubin was 420 μmol/L and the maternal unconjugated bilirubin level just prior to delivery was 480 μmol/L. His initial PCV was 40%, which, again, did not indicate that the hyperbilirubinaemia was due to haemolysis. His serum albumin level was within the normal range and arterial pH was maintained above 7.30. Phototherapy was commenced shortly after birth. A double-volume exchange transfusion was performed at six hours of age and resulted in a fall in the unconjugated bilirubin from 386 to 187 μmol/L. He received phototherapy for a further five days. He was slow to establish bottle feeding and was finally discharged at 20 days of age. He had a normal neurological examination. AABR was normal. An MRI scan at nine weeks of age showed normal myelination, without any evidence of bilirubin deposition. At 18 months of age, his neurological examination and all areas of his neurodevelopment, including speech and hearing, were normal.

Discussion

Congenital non-obstructive non-haemolytic unconjugated jaundice was first described by Crigler and Najjar in 1952 [1]. The condition has an autosomal recessive pattern of inheritance and has an incidence of less than one per million births. The mainstay of treatment of CN-1 is daily phototherapy, which can be required for up to 12 hours a day [8].

There have only been two previous reports of pregnancy resulting in a live-born infant in mothers with CN-1. In the first case, the infant was severely icteric at birth, with an umbilical cord unconjugated bilirubin level of 410 μmol/L [7]. He was treated with phototherapy and was subsequently reported to be quadriplegic at 18 months of age.

In the second case, the infant was delivered to a mother who had undergone daily phototherapy and fortnightly

albumin infusions [2]. This maintained the maternal bilirubinaemia between 230 and 280 μmol/L. At birth, the infant had a bilirubin of 250 μmol/L, which responded to phototherapy. The infant had normal development and brain MRI at four months of age. The control of maternal bilirubinaemia in this case was considerably better than in either of the mothers in the present report, where there was non-compliance with phototherapy.

The mechanism by which unconjugated bilirubin causes neurotoxicity is not known [3]. The precise level and duration of raised serum bilirubin at which permanent damage of the developing nervous system occurs is also unknown [10]. Vulnerability to the development of kernicterus is not only related to the level of unconjugated hyperbilirubinaemia, but is also related to other factors, including the concentration of serum albumin, serum pH and intactness of the blood–brain barrier [9].

Both of our cases at birth had bilirubin levels that were similar to their mothers', suggesting that the placenta did not present a barrier to unconjugated bilirubin entering the foetal circulation [2]. Indeed, in animal models, unconjugated bilirubin passively diffuses across the placenta [5].

The decision to undertake exchange transfusion could be considered to be controversial, given that the foetus had already been exposed to a high level of bilirubin for many months. However, the maternal levels of unconjugated bilirubin were particularly high, and it was felt that it was important to intervene rapidly. Despite, in case 1, there having been evidence of bilirubin deposition on the MRI scan soon after birth, he has not demonstrated any long-term consequences found after kernicterus, such as athetoid cerebral palsy or auditory impairment [9]. It has previously been described that changes in the globus pallidus compatible with kernicterus on MRI scan at birth can be associated with normal neurological findings at one year of age [4]. Although it was reassuring that case 2 had a normal AABR, an infant who had undergone an exchange transfusion at birth for hyperbilirubinaemia, had a normal AABR at 13 days of age, but had profound sensorineural hearing loss at seven months of age [11].

Hyperbilirubinaemia in the absence of haemolysis reduces the risk of long-term complications [6]. Neither of our cases had haemolysis as evidenced by their normal PCVs. This might explain, in part, the lack of a neurotoxic effect on the foetuses of the maternal bilirubin. Whether the exchange transfusion had any effect is debatable, but in both of our cases, the neurological outcomes have been favourable. Given the rarity of pregnancy in patients with CN-1, it is unlikely that enough patients can be recruited for a trial to discover whether exchange transfusions should be advocated in infants born to mothers with this condition.

Previously, we have recommended that pregnant women with CN-1 should terminate their pregnancies. In the light of our findings and the successful outcome in the other reported case [2], this has to be revisited.

In conclusion, we have described the treatment and follow-up of two infants born to mothers with CN-1. Both infants had exchange transfusions soon after birth, which might have contributed to their favourable neurodevelopmental outcomes.

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