CASE REPORT

Successful Pregnancy in a Crigler–Najjar Type I Patient Treated by Phototherapy and Semimonthly Albumin Infusions

VINCENT GAJDOS,* FRANÇOIS PETIT,‡ PASCALE TRIOCHE,* ALIX MOLLET–BOUDJEMLINE,* AURELIA CHAUVEAUD,§ ANNE MYARA,‖ FRANÇOIS TRIVIN,‖ JEANNE FRANCOUAL,‡ and PHILIPPE LABRUNE*

*Service de Pédiatrie, ‡Laboratoire de Biochimie Biologie Moléculaire, §Service de Gynécologie Obstétrique, Hôpital Antoine Béclère (APHP), Clamart, France; and ‖Laboratoire de Biochimie, Fondation Hôpital Saint Joseph, Paris, France

Crigler–Najjar (CN) syndrome is a congenital inborn error of hepatic bilirubin metabolism caused by the deficiency of bilirubin uridinediphosphate glucuronosyltransferase activity. The 2 types of CN can be distinguished based on their response to phenobarbital treatment. CN type I patients have profound unconjugated hyperbilirubinemia that does not respond to phenobarbital; they are at permanent risk for life-threatening bilirubin encephalopathy. Treatment of CN-1 disease relies on daily prolonged phototherapy (10–12 h/day). We report on a pregnancy in a CN-1 mother treated with intensive phototherapy and semimonthly albumin infusions. The mother gave birth to a healthy baby. Intensive management of pregnancy in CN-1 patients may result in a successful pregnancy.

Crigler–Najjar (CN) syndrome is a congenital inborn error of hepatic bilirubin metabolism caused by the deficiency of bilirubin uridinediphosphate glucuronosyltransferase activity (UGT1A1; EC 2.4.1.17). The 2 types of CN can be distinguished based on their response to phenobarbital treatment.[1] Although CN type I (CN-I; MIM#218800) patients have profound unconjugated hyperbilirubinemia that does not respond to phenobarbital, in CN type II (CN-II; MIM#143500) patients, phenobarbital significantly decreases hyperbilirubinemia. This difference is caused by the total loss of UGT1A1 activity in CN-I, whereas the loss is only partial in CN-II. CN-1 patients are at permanent risk for life-threatening bilirubin encephalopathy (kernicterus); a threshold accumulation of bilirubin in some brain regions may lead to neural dysfunction followed by cell death and permanent dysfunction. Treatment of CN-1 disease relies on daily prolonged phototherapy (10–12 h/day). To date, liver transplantation is the only curative treatment available.[2]

Pregnancy in CN patients is an exceptional event. It has been reported only once in a CN-1 mother[3] and 3 times in CN-2 mothers.[4–6] It is a therapeutic challenge because of the risk of bilirubin neurotoxicity for both mother and fetus. We report on a successful pregnancy in a young CN-1 mother treated with intensive phototherapy and semimonthly albumin infusions until delivery.

Case Report

A 28-year-old woman was regularly followed-up in our unit since birth for CN-1 syndrome. She was admitted on her first day of life for severe isolated unconjugated hyperbilirubinemia that required exchange transfusion. Daily phototherapy then was necessary to maintain the bilirubin serum concentration below the neurotoxic threshold; phenobarbital therapy was ineffective. At 4 months, the diagnosis of CN-1 was confirmed by enzymatic assay performed on liver tissue obtained by needle biopsy examination, showing a total deficiency of UGT activity. The patient then was discharged with home phototherapy for 10–12 hours per day with scheduled follow-up evaluation. After the identification of the UGT1A1 gene, molecular studies showed that the patient was homozygous for the c.923G>A mutation, which leads to the replacement of a glycine by a glutamic acid (p.Gly308Glu)[7]; the patient was found to have a wild-type promoter region (TA6/TA6) for the UGT1A1 gene. Except for cutaneomucous jaundice, physical examination proved normal throughout the evolution. Psychomotor development always proved normal. After graduating from high school, she went to the university where she succeeded in her studies and became a high-school Spanish teacher. At the age of 28 years, her first pregnancy began while her bilirubin serum concentration was 400 μmol/L (23.5 mg/dL), with a bilirubin/albumin molar ratio of .52. Given the likelihood of unconjugated bilirubin toxicity on the fetal brain, it was decided to intensify bilirubin reduction therapy. The number of phototherapy lamps was increased from 20 to 36 (with 20 blue-light lamps underneath the patient and 16 lamps above the patient). To maintain the free unconjugated fraction of serum bilirubin as low as possible, albumin infusions were performed every 2 weeks (1 g/kg body weight in 3 h). Bilirubin serum concentrations and bilirubin/albumin molar ratios were studied every 2 weeks, and bilirubin levels were monitored at home using a transcutaneous bilirubinometer. The evolution of biological data is shown on Figure 1; briefly, this combination of intensive phototherapy and semimonthly albumin infusions maintained the bilirubinemia between 230 and 280 μmol/L (13.5 and 16.5 mg/dL), and the bilirubin/albumin ratio remained less than .45 for the duration of the pregnancy (Figure 1).

At 12, 18, 22, and 32 weeks, fetal ultrasound examinations proved normal. At 32 weeks, fetal brain magnetic resonance

Abbreviations used in this paper: CN, Crigler–Najjar; CN-I, Crigler–Najjar type I; CN-II, Crigler–Najjar type II; UGT, uridinediphosphate glucuronosyltransferase.

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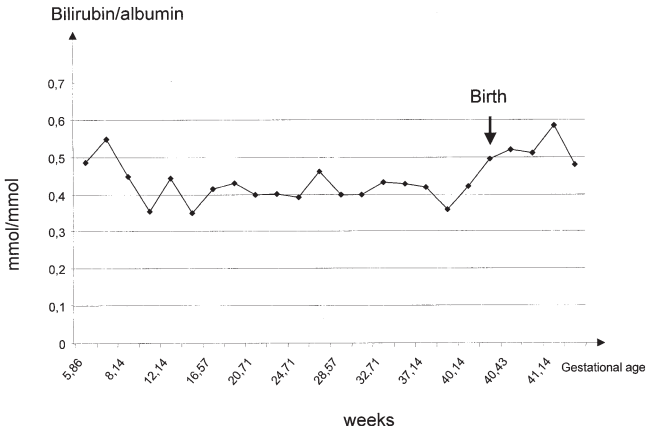

Figure 1. Follow-up evaluation of maternal bilirubin/albumin ratio during pregnancy and after delivery.

imaging was performed and found to be normal (not shown). At 39 weeks, the duration of daily phototherapy was increased to 14 hours a day. At 40 weeks and 3 days, an infant girl was born by cesarean section because of failure to progress. Her weight, height, and head circumference were 3460 g (60th percentile), 50 cm (50th percentile), and 35 cm (50th percentile), respectively. The Apgar score was 8 at 1 minute and 10 at 3 minutes. Except for jaundice, the physical examination proved normal. Because the bilirubin level was 250 μmol/L (14.7 mg/dL) at 1 hour of life, the neonate was placed under intensive phototherapy for 9 hours, resulting in a marked decrease of bilirubin serum concentration to 187 μmol/L (11 mg/dL). A second session of intensive phototherapy was prescribed at 22 hours of life for 4 hours because of another increase in bilirubin concentration to 230 μmol/L (13.5 mg/dL). During the following days, the infant's bilirubin levels continued to decrease: 215 μmol/L (12.6 mg/dL) on day 1, and 200 μmol/L (11.7 mg/dL) on day 2. The mother's bilirubin level increased slightly after birth to 315 μmol/L (18.5 mg/dL). The child was exclusively formula-fed since birth. On day 3, both automatic auditory-evoked potentials and a brain ultrasound were found to be normal in the infant. Mother and child (whose bilirubinemia was 165 μmol/L; 9.7 mg/dL) were discharged on day 6. On day 13, the infant weighed 4000 g; her height was 52.5 cm and her head circumference was 36 cm. The infant was drinking 6 bottles of 120 mL milk per day and, except for mild jaundice, had an entirely normal physical examination. The infant's serum bilirubin concentration was 118 μmol/L (6.9 mg/dL). The mother was jaundiced but normal otherwise, with a serum bilirubin level of 305 μmol/L (17.9 mg/dL) and a bilirubin/albumin ratio of .45. At the age of 7 weeks, physical examination of the infant proved entirely normal; weight and height were 5100 g (60th percentile) and 57.5 cm (60th percentile), respectively. The infant's bilirubin serum concentration was 21 μmol/L (1.2 mg/dL), and the mother's bilirubin serum concentration was 360 μmol/L (21.1 mg/dL) and the bilirubin/albumin molar ratio was .49. A magnetic resonance image of the brain was performed when the infant was 2 months of age, showing no abnormalities and normal basal ganglia and central nuclei. At the age of 4 months, physical examination of the child is still entirely normal, with normal psychomotor development (smile, tonus, and so forth).

Materials and Methods

At birth, the amniotic fluid was sampled. Blood was sampled at the same time in the mother, in the umbilical vein, in one of the umbilical arteries, and in the neonate. Serum total and conjugated bilirubin levels were measured using routine methods of the biochemistry department; total bilirubin concentrations in samples other than serum (amniotic fluid, meconium, colostrum) were measured by direct spectrophotometry. In all samples, the presence of bilirubin monoglucuronides and diglucuronides was assessed by high-performance liquid chromatography after alkaline methanolysis.[8]

Placental histologic examination was performed, including Hall staining (specific for bilirubin).

Results

The results of high-performance liquid chromatography blood analysis (in both the mother and the neonate) are shown in Table 1.

In the amniotic fluid, the bilirubin concentration was 2 μmol/L. In the first meconium (obtained at 2 hours), the bilirubin concentration was 840 nmol/g, (with 98.23% of unconjugated bilirubin, 1.72% of monoglucuronides, and .05% of diglucuronides); similar values were observed in a control meconium, sampled at 2 hours of life in a full-term healthy neonate whose mother was not jaundiced (940 nmol/g with 94.53% of unconjugated bilirubin, 5.07% of monoglucuronides, and .40% of diglucuronides). The bilirubin concentration in colostrum was 30 nmol/g (100% unconjugated) on day 0, and 10 nmol/g on day 2 (100% unconjugated).

The placental examination was normal.

Discussion

We report on a treatment regimen combining intensive phototherapy with albumin infusions every 2 weeks that successfully reduced the unconjugated bilirubin levels in a pregnant patient with CN-1 and prevented the development of

Table 1. Serum Bilirubin Concentrations at Birth in the Mother, the Umbilical Vessels, and the Neonate

	Total bilirubin, μmol/L	Unconjugated bilirubin, μmol/L	Unconjugated bilirubin HPLC, %	Monoglucuronides HPLC, %	Diglucuronides HPLC, %
Mother	242	242	100	0	0
Umbilical artery	222	222	99.80	.20	0
Umbilical vein	222	222	99.83	.17	0
Neonate	247	247	99.80	.20	0

NOTE. Bilirubin in mg/dL × 17.1 = bilirubin in μmol/L.
HPLC, high-performance liquid chromatography.

kernicterus in the infant. This regimen was designed to decrease total body exchangeable bilirubin and prevent its movements to extravascular sites. The fraction of bilirubin deposited in the brain and other tissues depends on its molar relationship with albumin binding sites and the dissociation rate of the bilirubin–albumin complex.[9] Furthermore, the use of the bilirubin/albumin molar ratio to monitor CN-1 patients has been shown to be useful and safe,[9] and, in our practice, we have been using it for more than 10 years in such patients. We wished to maintain this ratio at less than .6 because this value proved to be safe in neonates,[9] and, because of the poor knowledge regarding the potential neurotoxicity of bilirubin on the fetal brain, we tried to stay lower than .6 during the pregnancy. Because of the very low incidence of CN-1, we did not study the coding sequence of the UGT1A1 gene in the father and only found that he was homozygous for the wild-type promoter region (TA6/TA6). In connection with this, after discussion with both parents, we decided not to perform prenatal diagnosis. Fetal blood sampling was not considered to assess the eventual risk for kernicterus because of the absence of reliable data in such situations. At birth, the baby was icteric and both the baby and the mother had similar bilirubin serum concentrations. High-performance liquid chromatography analysis of bilirubin conjugates in the serum of the neonate, the mother, the umbilical artery, and the umbilical vein at birth were all similar. Jaundice slowly cleared in the baby after birth with minimal phototherapy.

Such an event is very rare and it has been reported only once previously[3]: phototherapy was not used for the mother, who had a grand mal seizure during labor and the baby was delivered by cesarean section. At birth, the baby was markedly icteric and treated with phototherapy. The child was said to be quadriplegic at 18 months. Successful outcomes of pregnancies (ie, healthy babies) have been reported in CN-2 mothers whose serum bilirubin concentrations were much lower[4-6]; furthermore, in 2 of these women, phototherapy and phenobarbital were used.[5,6]

Only a few reports have concerned infants who have been exposed in utero to high maternal bilirubin levels. Furhoff[10] reported normal outcomes in 133 children born to 58 mothers with either cholestasis or hepatitis-related jaundice during pregnancy; even though neither maternal nor infant bilirubinemias were specified in the report, it is likely that the majority of cases were related to conjugated hyperbilirubinemias. Similar results were reported by Roszkowski and Pizarek-Miedzinska.[11] In 1982, Waffarn et al[12] reported on a neonate born at 37 weeks to a mother with severe hyperbilirubinemia on the day before delivery (500 μmol/L with 220 μmol/L of unconjugated). The bilirubin concentration in the umbilical vein was 320 μmol/L (with 185 μmol/L of unconjugated). The neonate had severe neurologic manifestations and several exchange transfusions were performed. At the age of 2 years, the child was considered normal. This clinical report was highly suggestive of a potential neurotoxicity of bilirubin in the neonate.

In animals, data are scarce. An experimental study was conducted in pregnant -7J-1Ggousttheanimaedel
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Address requests for reprints to: Dr Philippe Labrune, Service de Pédiatrie, Hôpital Antoine Béclère (APHP), Clamart, France. e-mail: philippe.labrune@abc.aphp.fr; fax: (33) 1-45-37-40-20.