Scandinavian Journal of Gastroenterology, 2005; 40: 1124–1126

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CASE REPORT

Successful photo- and phenobarbital therapy during pregnancy in a woman with Crigler-Najjar syndrome type II

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Abstract
Severe hyperbilirubinemia in a pregnant mother suffering from Crigler-Najjar syndrome type II is a threat to the unborn child and may result in brain injury. We report the case of a Gly_{71} →Arg/Tyr_{486} →Asp homozygous mother of East Asian descent, who was treated with phototherapy during embryogenesis and with phenobarbital during the rest of the pregnancy. This resulted in significantly reduced bilirubin levels in the mother, who gave birth to a healthy boy. A neonatal hyperbilirubinemia resolved spontaneously.

Key Words: *Carbamazepine, Crigler-Najjar syndrome type II, kernicterus, phenobarbital, phototherapy, UGT1A1, unconjugated hyperbilirubinemia*

Introduction

Crigler-Najjar (CN) syndrome was first described in 1952 as an extreme form of familial non-hemolytic jaundice with kernicterus [1], and was later subdivided into two distinct entities [2]. In type I, the hepatic bilirubin-uridine-diphosphoglucuronate glucuronosyltransferase is completely inactive or absent. Affected individuals do not respond to phenobarbital therapy, and, without liver transplantation, usually die in infancy from kernicterus. In contrast, in type II CN, enzyme activity is present, but severely reduced, and patients survive into adulthood [3]. Kernicterus is rare in these patients, and phenobarbital therapy results in a significant enzyme induction.

Both conditions are due to autosomal recessively inherited mutations in the five exons of the UGT1A1 gene. In type I, the genetic defect results in a complete or near complete loss of enzymatic activity. This is usually the consequence of a stop codon or splice site mutation, which produces a truncated, inactive enzyme. In type II patients, in contrast, amino acid substitutions lead to a severely diminished enzyme activity, but not to a complete or almost complete lack of bilirubin glucuronidation, thus resulting in a milder phenotype with less extensively elevated serum levels of unconjugated bilirubin [3,4].

The overall prevalence of CN syndrome is unknown, but the disease is considered to be rare. Therefore, a pregnant female patient with this severe hyperbilirubinemia is hardly ever encountered in a hospital. Accordingly, only three cases with proven CN type II syndrome have been reported in the literature to date [5–7].

Pregnancy in CN type II patients is a therapeutic challenge because of the high risk of bilirubin encephalopathy with serious neurological damage as life-threatening complications for the fetus. In this report, we present the case of a pregnant woman with jaundice of unknown origin, in which the diagnosis of a CN syndrome type II due to the homozygous carrier state for a Gly_{71} →Arg and a Tyr486 →Asp substitution in the UGT1A1 isoform was made. Successive phototherapy and phenobarbital treatment led to a good fetal outcome.

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(Received 1 February 2005; accepted 5 March 2005)

ISSN 0036-5521 print/ISSN 1502-7708 online
DOI: 10.1080/00365510510025755

Case report

A 35-year-old woman (gravida 1, para 0), the daughter of Nepalese and Tibetan parents, was referred to our ambulant gastroenterological center because of jaundice at 10 weeks of pregnancy. Persistent moderate jaundice was noticed for the first time at the age of 10, when the patient still lived in India, but no specific diagnostic examinations were performed since then. With regard to her parents and her six siblings, the family history was unremarkable. In particular, there were no known hepatic disorders with jaundice.

The woman had no complaints at all. An abdominal ultrasound showed multiple small stones in the gallbladder, but no dilatated intra- or extrahepatic bile ducts. Laboratory examinations demonstrated a total serum bilirubin concentration of 8.9 mg/dl (normal <1.1 mg/dl) with an unconjugated bilirubin level of 8.6 mg/dl. Apart from a serologic status of healed hepatitis A and B virus infections, further extensive examinations (ALAT, ASAT, gamma-GT, AP, LDH, CHE, INR, serum electrophoresis, haptoglobin, ferritin, reticulocytes, serological markers of inflammation) did not reveal any additional abnormalities. Tests for HIV-1/2 infection and autoimmune antibodies (ANA, AMA, SMA, LKM, SLA, p- and c-ANCA, parietal cells, rheumatoid factor) were negative.

In order to prove the suspected diagnosis of CN syndrome type II, a sequence analysis of the five exons of the UGT1A1 gene was performed in the patient. The woman had inherited a complex allele with two mutations from both her parents. She was the double homozygous carrier of a glycine (GGA)-to-arginine (AGA) substitution at amino acid position 71, encoded by exon 1, and of a tyrosine (TAC)-to-asparagine (GAC) replacement at residue 486, encoded by exon 5. In the German husband and father of the child, a typical Gilbert syndrome [8] was ruled out by genomic analysis, as no TA insertion in the TATA box of the UGT1A1 promoter was detectable.

To reduce the serum bilirubin, we initially performed phototherapy for a total of 48 h during weeks 10 and 12 of gestation. As a result, bilirubin levels decreased to 6.0 mg/dl. Treatment with low-dose phenobarbital was initiated after completion of embryogenesis (adapted doses of 1×25 mg up to a maximum of 2×50 mg), thereby maintaining bilirubin levels in the range between 4.2 mg/dl and 5.2 mg/dl for the rest of pregnancy. The pregnancy then progressed without further complications, and regular fetal ultrasonic investigations were normal.

In the 40th week, the woman gave birth to a healthy boy (weight 3700 g, body length 52 cm, American Pediatric Gross Assessment Record (APGAR) index 10-10-10) via primary cesarean section due to a narrow pelvic inlet. The postpartal increased serum levels of unconjugated bilirubin (maximum of 5.8 mg/dl) in the infant dropped spontaneously to normal. No further complications occurred during the postpartal period. Echocardiographic and ultrasonic investigations of the encephalon, of the abdomen, and of the hips were normal. The now 5-month-old boy is well developed, and his serum bilirubin is normal.

Discussion

In our pregnant East Asian woman, suspected CN syndrome type II was confirmed by genomic analyses, demonstrating that she is a double homozygote for a $Gly_{71} \rightarrow Arg$ and a $Tyr_{486} \rightarrow Asp$ substitution, encoded by exons 1 and 5 of the UGT1A1 gene. A comparable genotype constellation has, so far, been described only once, in a 5-year-old Japanese boy, who was in addition the homozygous carrier of a $Leu_{132} \rightarrow Pro$ substitution encoded by exon 1 of the UGT1A1 gene [9]. For the prognosis of the fetus, it was also important to rule out the typical Gilbert syndrome TATA box mutation in the father of the child.

As maternally derived unconjugated bilirubin crosses the placental barrier by passive diffusion, the fetus is threatened by the highly elevated maternal bilirubin levels in CN type II, which may lead to neuronal and astrocytal degeneration. Fetal kernicterus or bilirubin-induced neurologic dysfunction can cause plegia, ataxia, central deafness, spasticity, mental retardation, choreoathetosis, seizures, or death. These complications have been commonly described in kernicterus of different etiologies [10] as well as in a case of untreated hyperbilirubinemia in a pregnant woman with CN syndrome type II (maternal bilirubin levels 17–21.8 mg/dl), leading to quadriplegia of the newborn [6]. Thus, bilirubin-lowering therapy in the pregnant mother is crucial to prevent brain injury of the fetus.

Daily phototherapy as performed in our case is the therapy of choice during embryogenesis. Treatment with phenobarbital should be avoided at this early stage of development. The drug is, however, commonly used during the rest of the pregnancy to induce enzyme activity. In two previously reported pregnancies of women with CN syndrome type II, low-dose administration of phenobarbital (maximal daily dose: 60 mg) beginning with the end of embryogenesis led to a good fetal outcome [5,7], as in our case. However, therapeutic experience concerning the use of phenobarbital in pregnancy is limited and has mostly been done in women with

epilepsy. One study reported a teratogenic risk of 3–5% in phenobarbital monotherapy during early pregnancy [11]. A recent pregnancy registry, however, showed a significant higher rate of major malformations in pregnancies with exposure to phenobarbital monotherapy in comparison with the background rate [12]. In addition, experimental findings revealed evidence that different antiepileptic drugs including phenobarbital cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans [13,14]. Although it is as yet unclear, whether the results of these animal studies have clinical significance in human beings and the use of alternative substances has not been evaluated to date, enzyme induction with phenobarbital in pregnant women with hyperbilirubinemia should be viewed with some concern.

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