INTRODUCTION

The Crigler-Najjar syndrome (CNS) is a disorder characterized by familial chronic nonhemolytic unconjugated hyperbilirubinemia caused by genetic lesions, which has two distinct forms: type I and type II. It has been pointed out that the inheritance of CNS type II could be explained in terms of both newborn and recessive traits (1), while type I has an autosomal recessive transmission (2). Clinically negligible Gilbert’s syndrome is the other familial unconjugated hyperbilirubinemia disorder, with an estimated incidence of 3-10% of the population (3). Bilirubin-UDP-glucuronyltransferase (UGT) is involved in the detoxification of bilirubin by conjugation with glucuronic acid in the endoplasmic reticulum of hepatocytes. Thus, water-soluble conjugated bilirubin is excreted by the hepatocyte with bile. The bilirubin UGT activity is absent in type I, while present in less than 10% in type II (4). CNS type I patients suffer from a very severe hyperbilirubinemia, which often causes death during the first months of life (5), and they need liver transplantation. On the other hand, in the presence of severe hyperbilirubinemia in CNS type II, a fetus is at risk for kernicterus (6). In type II, treatment options are conducted experimentally by some authors (7-9), while others do not agree with the necessity of treatment (10); however, these patients are at risk of encephalopathy when some conditions (anesthetics, drug use or severe infections, etc.) occur.

Crigler-Najjar syndrome is a rare disorder. The prevalence of CNS is unknown in various populations. We could not find any CNS case in the literature reported from Turkey to date. Schwegler et al. reported that chlofibrate treatment might dec-
increase the bilirubin level significantly in this syndrome (9). We administered fenofibrate treatment to two patients with CNS type II and report herein the results from our clinic.

CASE REPORTS

Case 1
A 15-year-old male student was admitted to our clinic because of jaundice, and he expressed self-conscious of his appearance. There was no history of white-colored stools or pruritus. He was noticed to have jaundice in his first year of life, which became more obvious when current illness was present. He was diagnosed as Gilbert’s syndrome three years ago, but had not taken any medication thus far. He had mumps two years ago. His brother had jaundice during the first year of his life but it disappeared two years later. His parents were not in a consanguineous marriage. Physical examination revealed deep icterus in sclera and skin. Liver and spleen were not palpable. Laboratory studies: urinary examination was negative for bile pigment, peripheral white blood cell count: 8.8x10⁹/L, red blood cell count: 5.6 million cells/µL, hemoglobin: 14.7 g/dl, hematocrit: 43.6%, platelet count: 336,000, mean corpuscular volume: 80 fl, mean corpuscular hemoglobin concentration: 29 g/dl, erythrocyte sedimentation rate: 23 mm/h, total bilirubin: 19.7 mg/dl, indirect bilirubin: 19.1 mg/dl, alkaline phosphatase: 118 IU/L, albumin: 4.6 g/dl, alanine aminotransferase: 12 U/L, aspartate aminotransferase: 19 U/L, prothrombin time: 13 seconds, lactate dehydrogenase: 157 IU/L, amylase: 90 IU/L, thyroid stimulating hormone: 2.4 µU/ml, free thyroxine: 6.3 µU/ml, and hepatitis B virus antigen (HBsAg) and anti-hepatitis C virus antibody (anti-HCV) were negative. Peripheral blood smear, hemoglobin electrophoresis, abdominal ultrasonography and upper gastrointestinal endoscopy revealed normal findings. Reticulocyte number was 1%, and Coombs tests were negative. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was absent by qualitative test. There was conjugated bilirubin in patient’s bile which we obtained from duodenal aspirate. The liver biopsy revealed nonspecific histological findings. The patient was subjected to phenobarbital challenge test (2 mg/kg/day for 3 days p.o.), and an appreciable fall in bilirubin occurred at the end of treatment (a 27% decrease in indirect bilirubin level) (summarized in Table 1). By the conclusion of our investigations, we had excluded all disorders which could be responsible for markedly high indirect hyperbilirubinemia. We then administered fenofibrate treatment (250 mg/day p.o.) for one month. At the end of treatment, serum indirect bilirubin was found to be unchanged from the pre-treatment level (14.2 vs 14.5 mg/dl) (summarized in Table 2).

<table>
<thead>
<tr>
<th>Total bilirubin in PB test (mg/dl)</th>
<th>Before PB</th>
<th>After PB</th>
<th>Rate of decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>21.5</td>
<td>13.7</td>
<td>27%</td>
</tr>
<tr>
<td>Case 2</td>
<td>19.0</td>
<td>14.0</td>
<td>26%</td>
</tr>
</tbody>
</table>

Table 1. Results of phenobarbital loading tests

<table>
<thead>
<tr>
<th>Total bilirubin in FF treatment (mg/dl)</th>
<th>Before FF</th>
<th>After FF</th>
<th>Rate of decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>14.2</td>
<td>14.5</td>
<td>Insignificant</td>
</tr>
<tr>
<td>Case 2</td>
<td>19.0</td>
<td>18.2</td>
<td>Insignificant</td>
</tr>
</tbody>
</table>

Table 2. Results of fenofibrate treatment

Case 2
A 34-year-old female patient had been suffering from jaundice and back pain. Her jaundice had persisted since birth. She had a history of nonsteroidal anti-inflammatory drug use for the back pain. There was no disease in her parents. Her brother died due to severe jaundice six months following birth. On physical examination, there was deep icterus in her sclera and skin, and thyroid gland was palpable. Laboratory findings: urinary examination revealed trace bilirubin, peripheral white blood cell count: 5.4 million cells/µL, white blood cell count: 9.3x10⁹/L, platelet count: 349,000/mm³, hemoglobin: 14.1 g/dl, hematocrit: 41.2%, mean corpuscular volume: 82 fl, mean corpuscular hemoglobin concentration: 33 g/dl, erythrocyte sedimentation rate: 29 mm/h, total bilirubin: 19 mg/dl, indirect bilirubin: 18.1 mg/dl, alkaline phosphatase: 76 IU/L, albumin: 3.9 g/dl, alanine aminotransferase: 33 U/L, aspartate aminotransferase: 21 U/L, lactate dehydrogenase: 78 IU/L, amylase: 56 IU/L, prothrombin time: 14 seconds, thyroid stimulating hormone: 1.7 µU/ml, free thyroxine: 4.3 µU/ml, and reticulocyte 1%. Peripheral blood smear and hemoglobin electrophoresis were normal, and tests for hemolysis were negative. G6PD deficiency was found to be negati-
ve using qualitative test. HBsAg, anti-HCV, anti-thyroglobulin and anti-microsomal antibody were also negative, and abdominal ultrasonography and upper gastrointestinal endoscopy revealed normal findings. We found conjugated bilirubin in patient's bile obtained from duodenal aspirate. Thyroid ultrasonography and scanning were compatible with multinodular goiter. There was no specific finding in her liver biopsy. The phenobarbital challenge test showed decrease in indirect bilirubin level from 19 to 14 mg/dl (26%) in three days (2 mg/kg/day p.o.) (summarized in Table 1). We administered fenofibrate treatment (250 mg/day) for one month, but bilirubin level showed no change (19 vs 18.2 mg/dl) (summarized in Table 2).

**DISCUSSION**

Persistent jaundice is present at or soon after birth in CNS type I, and the untreated patient is uniformly lethal by the age of two years, secondary to kernicterus. Jaundice may not manifest until later in infancy or childhood in CNS type II. Phenobarbital loading test (5 or 7 days per oral) is used to discriminate between types I and II (11, 12). In CNS type II, serum bilirubin levels respond to phenobarbital (enzyme-inducing agent) treatment with a decrease of at least 25%, especially after the second half of the first year (4). However, in one report, two patients with CNS type II did not respond to phenobarbital treatment because this drug did not enhance the expression of bilirubin-UGT1; (11); therefore, it is important to characterize the genetic defect in this condition. Serum bilirubin concentrations may decrease to normal levels in patients with Gilbert's syndrome with phenobarbital treatment, but the levels in patients with CNS type II do not reach normal range (12). On the other hand, as a rule, no response is seen in patients with CNS type I. The serum bilirubin level rarely exceeds 3-4 mg/dl in Gilbert's syndrome, while it ranges from 0.3 to 1.0 mg/dl in normal subjects. In CNS type II, serum bilirubin level ranges from 6 to 20 mg/dl and the majority of patients survive into adulthood without complications (3). This range is wider (15-50 mg/dl) in type I (14). In our cases, serum bilirubin level was markedly high and phenobarbital tests (with a shorter testing period of only 3 days) supported the diagnosis of CNS type II. Well-compensated hemolytic anemia, primary shunt hyperbilirubinemia, posthepatic or hyperbilirubinemia, and toxic drug reactions are some types of unconjugated hyperbilirubinemia in adults, and sometimes it is difficult to make a differential diagnosis. Hyperbilirubinemia in the presence of hemolysis rarely exceeds 3-4 mg/dl. G6PD deficiency is a common red cell enzyme disorder in the Mediterranean region. There was no sign of apparent hemolysis (a negative result for Coombs tests and qualitative G6PD deficiency test and no increase in reticulocyte number), portal hypertension, hepatitis or any drug use in our cases. To confirm diagnosis of CNS type II, UGT enzyme activity in liver biopsy can be measured. We could not measure hepatic glucuronyl transerase activity in the patients because of unavailable technical conditions in our country. Moreover, in addition to phenobarbital response, bile analysis is recommended. In CNS type I, duodenal bile is devoid of bilirubin conjugates, but in type II, bilirubin monooconjugates are present in bile (15). We found bilirubin conjugates in our patients' bile and this finding also supported the diagnosis. Definitive diagnosis can be made by in vitro expression of mutant DNA from patient COS cells or fibroblasts, but this method is too elaborate and expensive for routine use (13).

The only effective treatment for CNS type I patients is orthotopic liver transplantation. Phototherapy is effective but not practical to use life-long. Drugs that interact with bilirubin metabolism, for instance, sulfonamides, salicylates or penicillin, should be avoided in patients with CNS types I and II. Recent experimental approaches suggest gene repair therapy (16) or liver cell transplantation. Although common belief leans towards no need to treat CNS type II patients, risk of neurological problems in severe hyperbilirubinemia warrants consideration. In addition, many adults are concerned about a good physical appearance in their social life. Treatment with low-dose phenobarbital is suggested in these patients (8). Schweger et al. reported that under treatment with chlofibrate, the serum total bilirubin was decreased significantly (9). In light of their results, we administered the other fibrate, fenofibrate, to our two patients, but this treatment did not decrease bilirubin levels. The predominant effect of fibrates is to activate lipoprotein lipase, which catalyzes triglyceride-rich lipoproteins, resulting in a reduction in triglyceride level (17). There is no standardized knowledge in the literature about the effect of fibrates on bilirubin-UGT activity,
and the mechanism of bilirubin decrease is not clear. It was reported in a study that fibrates induce hepatic peroxisome and mitochondrial proliferation in monkeys (18). It is still not known whether or not fibrates lower the bilirubin level. However, it is important to discover a new effective, long-term and useful drug to activate bilirubin-UGT in such patients.

REFERENCES