ESPGHAN 50th ANNUAL MEETING

of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition

Abstracts

10–13 May 2017

Prague · Czech Republic

Prague Congress Centre (PCC)

www.espghancongress.org

H-P-030

Do patients with Crigler-Najjar type 2 always need a life-lasting treatment with phenobarbital?

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Objectives and study: Crigler-Najjar type 2 (CN-2) is an autosomal recessive condition caused by mutations in UGT1A1 gene. In CN-2, uridine-di-phospho-glucoronosyl-transferase (UDPGT) enzyme activity is <10% of normal with a total serum bilirubin (TB) ranging from 6 to 20 mg/dl. Patients with CN-2 need a life-lasting treatment with phenobarbital due to a persistent risk of bilirubin encephalopathy.

Methods: We describe two brothers with an unusual CN-2 phenotype followed up respectively for 12 and 10 years.

Results: First patient was born at full term to non-consanguineous Italian parents. His medical history was remarkable for prolonged neonatal jaundice requiring phototherapy with a familial history of mild unconjugated hyperbilirubinemia in the mother. He was first seen at the age of 12 because of jaundice. Blood tests showed an increase of unconjugated bilirubin (TB 5.2 mg/dl, conjugated 0.56 mg/dl). Blood count, liver enzymes, haptoglobin, Coombs test and G6PDH activity were normal. Molecular analysis of UGT1A1 gene detected two heterozygous mutations (c.674T>G exon 1, c.I099C>T exon 4) and a heterozygous polymorphism $(TA)_7$ of TATA box. He was followed up without treatment. At age fourteen, an acute and abrupt increase of his jaundice was observed with a TB of 18.15 mg/dl. No infections, fasting or stressful events were reported. Phenobarbital was administered with remarkable decrease of bilirubin (TB 1.83 mg/dl) but the therapy was discontinued after few days due to nausea and drowsiness. After two months a further increase of TB to 8.38 mg/dl was detected and phenobarbital was restarted. No further jaundice episodes occurred, and TB maximum values were of 2.74 mg/dl. Due to the unusually low total bilirubin levels for a patient with CN-2, phenobarbital was progressively discontinued after about 2 years of persistent treatment. He was strictly followed up for seven years with a good and stable clinical condition and a TB between 3.7-7.8 mg/d. The second patient is the 13 year-old brother of first patient. At the age of 3 he was screened for unconjugated hyperbilirubinemia with a TB of 2.76 mg/dl (conjugated 0.44 mg/dl). Molecular analysis confirmed the same mutations of the propositus. During the following 10 years a mild and persistent unconjugated hyperbilirubinemia was noticed (TB maximum value of 4.85 mg/dl) without acute episodes of jaundice. No treatment was proposed and he is on strict follow-up. Our patients' UGT1A1 mutations have been previously described. The first (c.674T>G) was reported associated with a phenotype ranging from Gilbert and CN-2 syndrome when associated with $(TA)_7$ promoter or frameshift mutations respectively. The second (c.I099C>T) was reported in a compound heterozygous patient with a mild CN-2 phenotype.

Conclusion: CN-2 has a wide range of clinical phenotypes and genetic variability involving UGT1A1 gene exons and promoter. Our report suggest that in mild CN-2 phenotype, as in our patients, treatment with phenobarbital may be "on-demand" once carefully instructed patients and parents to perform parenteral phenobarbital administration, with total bilirubin dosing, in case of evident increase of jaundice.