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Two cases of constitutional unconjugated hyperbilirubinemia with marked retention of indocyanine green.

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Abstract

Two cases of chronic unconjugated hyperbilirubinemia and marked retention of indocyanine green (ICG) are described. Since bilirubin uridine diphosphate (UDP)-glucuronyl transferase activities were depressed in their liver, the patients seemed to have bilirubin metabolism similar to that in Gilbert's syndrome. However, the ICG fractional disappearance rates of the cases were rather low (0.018 and 0.019) compared to the rates reported for Gilbert's syndrome. These results suggest that the patients had a new metabolic disorder which results in constitutional unconjugated hyperbilirubinemia and ICG intolerance.

KEYWORDS: Gilbert's syndrome, indocyanine green, bilirubin

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—— BRIEF NOTE ——

TWO CASES OF CONSTITUTIONAL UNCONJUGATED HYPERBILIRUBINEMIA WITH MARKED RETENTION OF INDOCYANINE GREEN

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Abstract. Two cases of chronic unconjugated hyperbilirubinemia and marked retention of indocyanine green (ICG) are described. Since bilirubin uridine diphosphate (UDP)-glucuronyl transferase activities were depressed in their liver, the patients seemed to have bilirubin metabolism similar to that in Gilbert's syndrome. However, the ICG fractional disappearance rates of the cases were rather low (0.018 and 0.019) compared to the rates reported for Gilbert's syndrome. These results suggest that the patients had a new metabolic disorder which results in constitutional unconjugated hyperbilirubinemia and ICG intolerance.

Key words : Gilbert's syndrome, indocyanine green, bilirubin.

Gilbert's syndrome is characterized by inherited, chronic unconjugated hyperbilirubinemia and scleral icterus without any other physical or laboratory abnormalities (1). The impairment of hepatic bilirubin clearance is essential for a diagnosis of Gilbert's syndrome, but hepatic clearance of organic anions other than bilirubin varies among patients with this disorder (2).

Intravenous loading of exogenous pigments, such as indocyanine green (ICG) and sulfobromophthalein (BSP), is commonly employed as a liver function test. Although there is a close relationship between the ICG and BSP test, some rare cases with normal liver function tests including normal BSP test and serum bilirubin concentration show marked retention of ICG; the so-called "constitutional ICG excretory defect" (3).

Two cases of chronic unconjugated hyperbilirubinemia with marked delay of ICG clearance and almost normal BSP retention are reported.

Case 1. KY, a 23-year-old male, was found to be jaundiced. The patient, his parents and four brothers had no previous history of liver disease nor jaundice. Ten months later, he was admitted to our department for further examinations. Physical examination revealed no abnormal signs except for scleral jaundice. Total and conjugated bilirubin levels were 2.45 and 0.69 mg/dl, respectively, and other routine liver function tests, peripheral blood pictures and red-cell osmotic fragility

and viability were normal. Nicotinic acid load and diet restriction were not performed. A liver specimen obtained by biopsy showed portal fibrosis without round-cell infiltration. Activity of hepatic bilirubin uridine diphosphate (UDP)-glucuronyl transferase, using 0.19 mM bilirubin as the substrate (4), was very low (0.064 μmol/g protein/min) compared with the activity of two control subjects with gastric cancer and chronic hepatitis (0.126 and 0.114, respectively).

As a result, he was diagnosed as having Gilbert's syndrome. The BSP retention rate 45 min (R_{45}BSP) after a single intravenous injection of 5.0 mg per kg of body weight was 2.8 % (normal, less than 2 %), whereas the ICG test after an injection of 0.5 mg per kg of body weight was markedly impaired. The ICG retention rate at 15 min (R_{15}ICG) was 83 % (normal, less than 10 %), and the plasma ICG fractional disappearance rate (K_{ICG}) was 0.018 (normal, 0.18-0.20).

Case 2. TO, a 23-year-old male, consulted a doctor for treatment of the common cold and was noted to have scleral jaundice. Total and conjugated bilirubin levels were 3.7 and 0.6 mg/dl, respectively, and other liver function tests were within normal limits. The patient, his parents and sister had no previous history of liver disease. The patient showed no abnormalities besides scleral jaundice. Peripheral blood pictures, red-cell osmotic fragility and viability, and liver function tests were normal except for continuous unconjugated hyperbilirubinemia. Biopsied liver showed portal fibrosis with mild round-cell infiltration. Bilirubin UDP-glucuronyl transferase activity was 0.015 μmol/g protein/min. The maximum increase in total bilirubin after an intravenous injection of 50 mg nicotinic acid was 1.9 mg/dl, and after diet restriction to 400 kcal/day for three days, it was 1.4 mg/dl. Thus, the patient was diagnosed as having Gilbert's syndrome. The R_{45}BSP was 3.9 % ; R_{15}ICG, 80.4 % and KICG, 0.019. The secretory transport maximum (Tm) at 0.38 mg/min, and the relative storage capacity (S) of ICG at 27 mg/mg %, determined according to Wheeler *et al.* (5), were lower than the reported normal values (0.89 and 329, respectively) (6). The K_{ICG} values of his father and mother were 0.14 and 0.18, respectively.

Organic anion clearances from the circulating plasma in patients with Gilbert's syndrome are reported to be within both the normal and abnormal ranges (2). Martn *et al.* (2) classified Gilbert's syndrome into 3 groups, GS I, II and III, according to the pattern of impairment in hepatic BSP metabolism. They observed that K_{ICG} is significantly reduced (0.173 ± 0.041) and BSP uptake is defective in GS III. Since detailed BSP kinetics was not studied, we cannot group our cases according to Martin's classification. In any case, the K_{ICG} values of our patients were much lower than those reported for Gilbert's syndrome.

Patients without major hepatic disorders except for severely delayed ICG clearance are categorized as those with the "constitutional ICG excretory defect". The markedly depressed transfer rate of ICG from plasma to liver is the main pathophysiological indication of constitutional ICG intolerance (2), and abnormal bilirubin metabolism probably is not related to this disorder (3).

Our two cases are characterized by metabolic defects of two different pigments in the liver: bilirubin metabolism, as in Gilbert's syndrome, and ICG intolerance, as in the "constitutional ICG excretory defect". Recently, five cases of constitutional unconjugated hyperbilirubinemia combined with ICG intolerance were reported (7), and this new functional disorder may differ from the conventional entities of Gilbert's syndrome and constitutional ICG intolerance. Since both Tm and S of ICG in the second case reported herein were depressed, the disorder of this case appears to be similar to that of the 5 cases above (7). More detailed investigations of organic anion metabolism in patients with constitutional unconjugated hyperbilirubinemia would clarify the pathogenesis of the disorder.

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