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Liver function and the diagnostic significance of conjugated cholic acid and chenodeoxycholic acid in serum of African patients with sickle cell disease

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Summary

Concentrations of two primary bile acids (cholic acid and chenodeoxycholic acid) were determined by radioimmunoassay in the serum of 15 African homozygous sickle cell patients, ages ranging from 4 to 22 years. The mean serum levels of the two primary bile acids studied were significantly elevated when compared with the normal mean values. About 67% of the patients had pathological elevation of both primary bile acids, thereby indicating some hepatobiliary damage. Serum conjugated cholic acid correlated significantly with serum chenodeoxycholic acid in the sickle cell disease ($r = 0.91$, $p < 0.001$). The results suggest that radioimmunoassays of serum conjugated cholic acid and chenodeoxycholic acid in sickle cell disease may also serve as useful biochemical assays in predicting liver dysfunction in sickle cell disease.

Key words: conjugated cholic acid; chenodeoxycholic acid; liver function; sickle cell patients.

Introduction

Bile acids are the final products of hepatic cholesterol metabolism and after conjugation with glycine or taurine, are excreted into the bile. Nearly all the metabolic reactions in the formation and conjugation of bile acids take place within the hepatic cell and as a result, there are likely to be changes in bile acid composition, in biliary excretion of bile acids and in their accumulation in blood in connection with liver disease. Several studies have shown that serum bile acid concentration is a sensitive indicator of liver function and that greatly

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increased bile acid concentrations are seen in sera of patients with hepatobiliary diseases (Korman et al., 1974; Barnes et al., 1975; Hepner and Demers, 1977; Laatikainen and Ikonen, 1977; Lindblad et al., 1977; Skrede et al., 1978; Stiehl et al., 1978).

Tests of liver function including serum transaminases, alkaline phosphatase, leucine aminopeptidase, lactic acid dehydrogenase (LDH) and bilirubin are elevated in a certain proportion of patients with sickle cell disease (Rosenblate et al., 1970). However, serum transaminases, alkaline phosphatase, leucine aminopeptidase, LDH, bilirubin are also known to be elevated in haemolytic and other disease conditions and they are rarely tissue-specific and may be elevated in tissue damage other than the liver (Sherlock, 1981; Rosenblate et al., 1970). Hence liver function studies in sickle cell disease, using these parameters have yielded equivocal results regarding the state of the liver.

It is known that bile acid elevations are specific to liver disease (Korman et al., 1974; Stiehl et al., 1978). It is therefore of interest to study the state of the liver in sickle cell disease using the radioimmunological technique to measure serum conjugated cholic acid and chenodeoxycholic acid in Nigerian patients with this disease.

Patients and Methods

A total of 15 sickle cell disease patients ranging in age from 4–22 years, with a mean age of 11.7 years were examined. A reference control group of fifteen healthy Nigerians with a mean age of 11.2 years were also investigated. The patients were first seen in the outpatient clinic of the University of Ife Teaching Hospital. All the patients were relatively asymptomatic at the time blood samples were taken for the assays. The only complaints were of moderate lassitude. Icterus was mild, but the liver was palpable in 9, or 60%, of these patients. There was no history or evidence of intrinsic liver disease in the patients. The diagnosis of sickle cell disease was based on clinical ground and confirmed by the finding of a haemoglobin SS pattern on cellulose acetate strips electrophoresis in the laboratory, after preliminary investigation had revealed very low haemoglobin and haematocrit values. All the control subjects had haemoglobin AA and no evidence of liver disease.

Serum samples. In both patients and controls serum samples were obtained 4 h after breakfast. These sera were stored frozen at -20°C until assayed for conjugated cholic acid and chenodeoxycholic acid, respectively.

Radioimmunoassay of bile acids in serum. Conjugated cholic acid and chenodeoxycholic acid were separately measured from the serum by radioimmunoassay (RIA) (Nordiclab Ltd., Oulu, Finland), utilizing ^{125}I -labelled bile acid derivatives as the ligand. The protocol used in the RIA was a slight modification of previously described methods of Maentausta and Janne (1979). All measurements were performed in duplicate.

Haemoglobin electrophoresis. This was performed on cellulose acetate strips according to Dacie and Lewis (1968).

Bilirubin. The estimation was done according to the method of Malloy and Evelyn in Varley (1968).

Serum enzyme. Serum alanine aminotransferase (ALAT) level was determined using the colorimetric method of Reitman and Frankel in Wooton (1964).

Serum protein. The Biuret method used for protein determination was according to Wooton (1964).

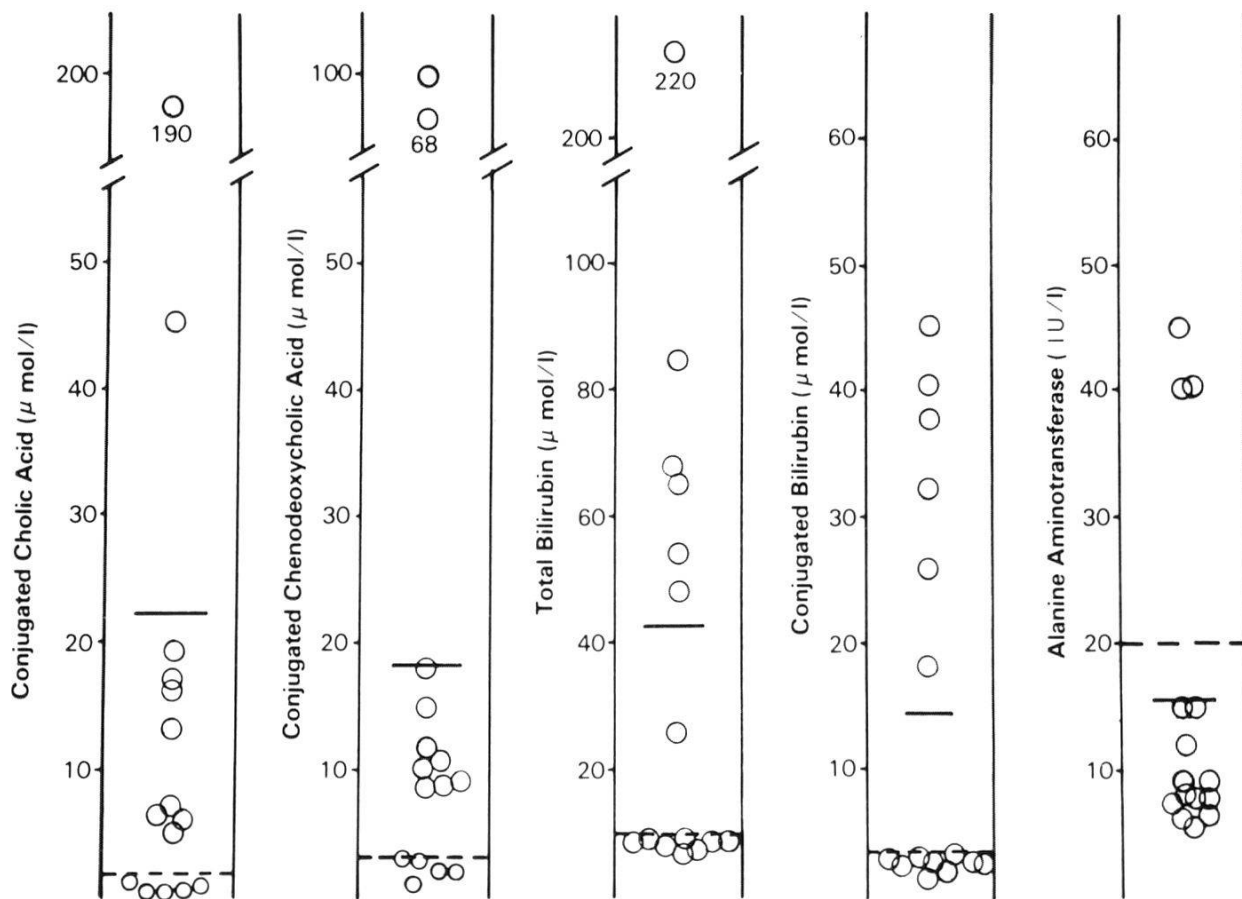


Fig. 1. Conjugated cholic acid (CCA), conjugated chenodeoxycholic acid (CDCA), bilirubin (total and conjugated) and serum alanine aminotransferase (ALAT) in patients with sickle cell disease. The horizontal dashed line indicates the limit of the mean + 2 SD (standard deviation) of the controls, the short solid lines the means for the patient group.

Results

The mean serum concentrations of the conjugated bile acids, bilirubin, alanine aminotransferase and protein in patients with sickle cell disease were as follows: conjugated cholic acid (CCA) $22.21 \pm 47.8 \mu\text{mol/l}$; conjugated chenodeoxycholic acid (CDCA) $18.36 \pm 27.8 \mu\text{mol/l}$; total bilirubin $42.86 \pm 55.8 \mu\text{mol/l}$; conjugated bilirubin $14.23 \pm 15.6 \mu\text{mol/l}$; alanine aminotransferase (ALAT) $15.60 \pm 14.2 \text{ IU/l}$, and serum protein, total 7.86 ± 0.39 , albumin 4.52 ± 0.37 . For the control group the mean values were $0.97 \pm 0.53 \mu\text{mol/l}$ for the CCA; $1.71 \pm 0.81 \mu\text{mol/l}$ for CDCA; $10.2 \pm 0.2 \mu\text{mol/l}$ for total bilirubin; $3.50 \pm 0.10 \mu\text{mol/l}$ for conjugated bilirubin; $14.82 \pm 2.76 \text{ IU/l}$ for ALAT; $7.49 \pm 0.53 \text{ g/100 ml}$ for total serum protein and $4.42 \pm 0.35 \text{ g/100 ml}$ for albumin.

About 67% or 10 of the cases of sickle cell disease studied had significant elevated values of serum conjugated cholic acid (CCA) and chenodeoxycholic acid (CDCA) (see Fig. 1). Raised bilirubin levels were seen in 7 patients or 46% of all the sickle cell disease patients studied. The concentration varied from

patient to patient but the highest value seen was 220 $\mu\text{mol/l}$ (Fig. 1). Elevated individual values of ALAT were observed in 3 out of 15 sickle cell disease patients, but the mean activity was not significantly elevated ($p < 0.10$) (Fig. 1). All patients had serum total protein and albumin values that were within the control level.

Correlations between the conjugated bile acids and the liver function tests

There was a highly significant ($r = 0.91$, $p < 0.001$) correlation between CCA and CDCA; ($r = 0.68$, $p < 0.005$) between CCA and conjugated bilirubin; ($r = 0.76$, $p < 0.001$) between CDCA and conjugated bilirubin; ($r = 0.66$, $p < 0.005$) between CCG and ALAT and ($r = 0.57$, $p < 0.01$) between CDCA and ALAT but no correlation was found between the conjugated bile acids and other liver function tests within the group of patients studied.

Discussion

A number of investigators have indicated that serum bile acid determinations are more sensitive than any other conventional laboratory test to reveal an occult liver disease (Korman et al., 1974; Barnes et al., 1975; Stiehl et al., 1978). They have found that serum bile acid assay very often provide earlier information about disturbed liver function in disease state than what is achieved with determinations of serum transaminases, LDH, alkaline phosphatase, bilirubin, leucine aminopeptidase and prothrombin time (Korman et al., 1974; Stiehl et al., 1978; Matern and Gerok, 1978).

Although there are a number of studies dealing with the macroscopic and microscopic appearances of the liver in sickle cell disease, very little is known about the biochemical sequences of this disease at the cellular level, and no data has been reported on the serum levels of conjugated cholic acid and chenodeoxycholic acid. Since most of the previous studies were based on determinations of serum enzymes and other liver function tests (Rosenblate et al., 1970; Isichei, 1980), which are not tissue-specific and less sensitive, it is possible that most of the patients may be unidentified.

This study has shown that the mean serum concentrations of CCA and CDCA in African patients with sickle cell disease are significantly higher ($p < 0.001$) than the concentrations found in healthy African controls. The abnormally high values were found in young patients which seem to suggest that age may well be an important determinant of hepatocellular dysfunction in this disease. This may be due to the cumulative effect of a continuous assault on the liver by repeated crises which then cause hepatic damage and lead to gross changes with their biochemical effects. Some of these patients with elevated conjugated bile acids also had increase values of other liver function tests.

The mechanism of this hepatobiliary dysfunction appears to include the stasis of sickled erythrocytes in the liver sinusoids combined with swelling of the

Kupffer cells. These would lead to varying degrees of ischemia, coagulation necrosis of liver cells and bile stasis. In addition to the possible vascular causes of the parenchymal lesions, it is interesting to postulate that during crises and/or periods of hemolysis, a "toxic agent" possibly liberated as the result of antigen-antibody reaction may act as a hepatotoxin and be responsible for some of the parenchymal changes seen in livers of patients with sickle cell disease (Bogoch et al., 1955).

Bile plugs are sometimes seen at liver biopsy and sickle cell appears to be one cause of intrahepatic cholestasis (Klion et al., 1964). Cholelithiasis and chronic cholecystitis has been reported in 25–33% of sickle cell patients even though less than 10% had signs and symptoms of these complications (Barret-Connor, 1968).

In conclusion it appears from our observations that liver disease in sickle cell disease occurs more frequently than conventional liver function studies have previously indicated (Isichei, 1980; Rosenblate et al., 1970).

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