IMPAIRED METABOLISM OF METHIONINE IN SEVERE LIVER DISEASES

I. CLINICAL AND PATHOPHYSIOLOGICAL SIGNIFICANCE OF ELEVATED SERUM METHIONINE LEVELS

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Summary

Serum methionine levels increased to a greater extent in patients with severe liver diseases such as fulminant hepatitis and liver cirrhosis with and without hepatic encephalopathy. However, the concentrations remained unchanged in non-encephalopathic cirrhotic cases associated with hepatocellular carcinoma, and their serum methionine levels increased only moderately even at the time of encephalopathy. At least two different mechanisms of serum methionine elevations, possibly due to release from injured hepatocytes or diminished catabolisms of this amino acid in the damaged liver, could be differentiated; the former would be involved mainly in fulminant hepatitis and the latter in liver cirrhosis. A methionine-loading test performed in cirrhotic patients supported the validity of these considerations. No significant increase of serum methionine levels in cirrhotic patients with hepatocellular carcinoma was observed, possibly by remarkable consumption of this amino acid in hepatoma tissues. During the clinical course of several patients, serial determinations of serum methionine concentrations indicated that the levels varied depending upon alterations in the pathophysiological state of the damaged liver; much higher levels were observed concomitantly with decompensated signs such as ascites, jaundice and hepatic encephalopathy. These results suggest that monitoring of serum methionine levels would be very valuable, especially for judging prognosis and predicting hepatic encephalopathy in severe liver disease.

Key Words: serum methionine, a methionine-loading test, severe liver disease, hepatic encephalopathy, hepatic failure, methionine metabolism.

Introduction

Several papers1-3) recently published on abnormal serum aminogram in patients with fulminant hepatitis or liver cirrhosis have described that methionine is one of the amino acids which markedly increased in the circulating blood. The toxic effects of methionine and its derivatives on various functions of the central nervous system have been reported in clinical4) and experimental studies5,6). Methionine is well known to be catabolized exclusively in the liver, but little is known about impaired metabolism of this essential amino acid in patients with liver disease.
In this communication, the clinical significance of monitoring serum methionine levels in patients with fulminant hepatitis or liver cirrhosis is shown. Serial determinations of increased methionine levels, resulting from impaired metabolisms in patients with liver cirrhosis were determined by methionine-loading test.

Subjects and Methods

The clinical subjects of this study were as follows: 14 patients with fulminant hepatitis (male 6, female 8); 50 cirrhotics, 18 with hepatic encephalopathy (male 15, female 3) and 32 without encephalopathy (male 25, female 7); 25 hepatoma-bearing cirrhotics, 7 with encephalopathy (male 6, female 1) and 18 without hepatic encephalopathy (male 18); and 20 control subjects (male 15, female 5). These patients were admitted to Okayama University Hospital from January 1977 through July 1980. Fulminant hepatitis was diagnosed according to the criteria which has been used widely in Japan. Diagnosis of liver cirrhosis was made by means of peritoneoscopic and histologic findings of the damaged liver, and hepatocellular carcinoma (abbreviated as hepatoma in the latter part of this paper) was finally confirmed by autopsy. Hepatic encephalopathy described in this study indicates apparent neuropsychiatric symptoms, i.e. severer than Grade II in classification of Sherlock.

The blood sampling for amino acid analysis in patients without encephalopathy was done in the early morning, and in patients with hepatic encephalopathy before treatment. The serum thus obtained was stored as −20°C until amino acid assays were performed, within several days unless otherwise stated. Determinations of neutral amino acid, including methionine, were carried out according to two different procedures as already published, by which comparable levels of these amino acids could be obtained. Biochemical laboratory tests for liver function were performed routinely.

An intravenous methionine-loading test with a dose of 10 mg per kg body weight was carried out in 17 cases with compensated cirrhosis, and 5 healthy control subjects, the procedure detailed in abstract form. Serum methionine levels taken at 30 and 45 minutes following single intravenous administration of methionine were plotted on a semi-logarithmic graph, and Kmet value was calculated by a ratio of 0.693 divided by half time in minutes of methionine clearance from the circulating blood. The data obtained were statistically analyzed, and significant probability of the mean was evaluated by Student t-test.

Results

Serum methionine levels in patients with severe liver disease

Serum methionine concentrations increased to various extents in patients with fulminant hepatitis and in cirrhotics without hepatoma (Table 1). The levels were much higher in patients with fulminant hepatitis than those with liver cirrhosis. In non-encephalopathic cirrhotic patients, significant difference (p<0.05) in serum methionine levels was observed between cases associated with hepatoma (27 ± 21...