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Concentration of prothrombin fragment 1+2 (F1+2) in patients with liver cirrhosis and chronic hepatitis C infection

Liver is a site where the prothrombin complex factors, like prothrombin (factor II), factor VII, factor IX and factor X, which participate in an activation of coagulation system, are synthesized. Prothrombin circulates in the blood and lymph as an inactive zymogen. In the presence of calcium ions it interacts with having negative charge phospholipids of cell membrane, and together with factor Va, it makes up a prothrombinase complex, which next creates, with participation of factor Xa, thrombin, endopeptidase relatively selective to fibrinogen. As a result of prothrombinase's activity on prothrombin fragment F1+2 is split off and simultaneously prothrombin 2 is released. Appreciation of serum concentration of prothrombin complex factors is a very sensitive indicator of liver synthesis activity. It is also a very valuable way to estimate the stage and seriousness of inflammatory processes, a toxic damage and the cirrhosis of liver.

The aim of this study was to assess the serum concentration of F1+2 in patients with liver cirrhosis developed during HCV infection and in patients with chronic hepatitis C infection (CHC).

MATERIAL AND METHODS

The study group consisted of 52 patients hospitalised at the Department of Infectious Diseases of Medical University of Lublin, Poland. Among them, 18 patients (8 men and 10 women), aged 19–59 years, had a stable liver cirrhosis and 34 patients (21 men and 13 women), aged 20–41 years, were diagnosed with chronic hepatitis C infection. The diagnosis of liver cirrhosis in the course of HCV infection was made on the presence of HCV RNA in serum in RT-PCR and on the liver biopsy results in Child-Plough classification. All patients with CHC met the criteria for standard antiviral therapy and they began to be treated with interferon alpha and Ribavirin, without having any concomitant diseases. The control group consisted of 25 healthy individuals (13 men and 12 women), aged 19–60 years. Blood samples were obtained from ulnar veins of patients being on empty stomach into the tubes containing 3.8% solution of citric acid diluted 1:10. They were then centrifuged for 15 min at the speed of 1500/min and room temperature. The plasma was kept at the temperature of –40°C before being tested. The serum concentration of F1+2 was determined by the immunoenzymatic assay Enzygnost F1+2 micro. The obtained data were statistically evaluated with Kolmogorow-Smirnow test assuming 5% risk of conclusion error.

RESULTS

Statistical test showed that data spreads in the usual way. The serum concentration of F1+2 was 1.1 ± 0.6 nmol/l in the control group, 1.078 ± 0.485 nmol/l in the cirrhotic patients and 1.438±784 nmol/l in the patients with CHC (Tab.1). There were no statistically significant differences in the serum concentration of F1+2 between cirrhotic patients and controls ($p > 0.05$). Similarly, the differences observed in the F1+2 levels in patients with CHC and controls were not statistically important ($p > 0.05$). No statistically significant differences were observed in the F1+2 serum concentration between patients with cirrhosis and CHC ($p > 0.05$). In general, elevated serum levels of F1+2, above 1.7 nmol/l, were observed in every third patient, however, more often in patients with CHC (35.3%) than in cirrhotic patients (16.7%).

Table 1. Concentration of prothrombin fragment F1+2 in the examined group

	n	F1+2	
		X	SD
Chronic hepatitis	34	1.438	0.784
Cirrhosis	18	1.078	0.485
Control group	25	1.1	0.6

n – number of patients, X – arithmetical mean, SD – standard deviation

DISCUSSION

A variety of laboratory abnormalities of the hemostatic system have been reported in patients with liver cirrhosis. Since most of these abnormalities indicate a hypocoagulable and hyperfibrinolytic state, they have long been linked to the high bleeding tendency among these patients. Both hypocoagulation and hyperfibrinolysis can easily be explained by reduced hepatic synthesis of several coagulation factors and the main fibrinolysis inhibitors tissue plasminogen activator inhibitor and α2-antiplasmin (1, 4, 7, 10, 13, 15).

In addition to its synthetic function, the liver is the key site for clearance of activated clotting and fibrinolytic factors and complexes, e.g., thrombin-antithrombin (TAT) and plasmin-antiplasmin (PAP) complexes. Other coagulation and fibrinolytic inhibitors such as antithrombin III (AT III) and α2-antiplasmin are also synthesized in the liver and their deficiency may result in bleeding or thrombotic complications. Exceptions are von Willebrand factor (vWf), tissue plasminogen activator (tPA), and type I plasminogen activator inhibitor (PAI-1), which are derived predominantly from endothelial cells (2, 6, 8, 9, 14).

For assessment of hyperfibrinolytic state the following molecular markers of activation of coagulation: prothrombin fragment F1+2 and thrombin-antithrombin III complexes, are helpful. Our results show that the serum concentration of F1+2 was 1.1 ± 0.6 nmol/l in the control group, which is consistent with the data from the literature. (3, 5, 11). We did not observe any significant differences in the serum concentration of F1+2 in neither patients with stable cirrhosis nor in those with chronic hepatitis C as compared to the control group. On tests of thrombin generation: thrombin-antithrombin complexes, fibrin(ogen) degradation products, and prothrombin fragments 1+2 were not found to be significantly different from an age- and gender- matched control group, whereas albumin, factor V, fibrinogen, antithrombin III, and α2-antiplasmin were all significantly low, reflecting reduced synthetic function and correlation in ascitic and non-ascitic patients. There was no correlation between impaired

synthesis (antithrombin III and α2-antiplasmin) and indices of DIC (prothrombin fragment 1+2, thrombin-antithrombin complexes, and XDP). The percentage of patients with high prothrombin fragments F1+2 and thrombin antithrombin levels in each Child grade group was similar (2). However, it seems interesting that in 16.7% of patients with cirrhosis and in more than every third patient with CHC serum levels of F1+2 were elevated, which may suggest an activation of coagulation in both examined groups.

Hypercoagulation in cirrhotic patients is still a subject of controversy. On the one hand, patients with cirrhosis are at increased risk of disseminated intravascular coagulation, but on the other hand, there is a reason to question whether DIC is a frequent component of the coagulopathy of cirrhosis. A major contribution of hypercoagulation to the coagulopathy of cirrhotic patients has been rejected based on the finding of lower activation markers than in patients with DIC suffering from malignancies and/or sepsis (12, 15). Simultaneously, data in the present literature confirm that DIC is not a common feature of stable liver cirrhosis, and some of the laboratory findings suggestive of DIC are predominantly a reflection of decreased hepatic clearance of activation products by the reticuloendothelial system of the diseases liver (2).

CONCLUSIONS

There were no statistically significant differences observed in serum concentration of F1+2, both in patients with stable cirrhosis and with CHC, compared to controls. However, in 16.7% of patients with cirrhosis and in 35.3% of patients with CHC elevated serum levels of F1+2 were observed.

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SUMMARY

The aim of this study was to assess the serum concentration of F1+2 in patients with liver cirrhosis developed during HCV infection and in patients with chronic hepatitis C infection. The study group consisted of 52 patients hospitalised at the Department of Infectious Diseases of Medical University of Lublin, Poland. Among them, 18 patients (8 men and 10 women), aged 19–59 years, had a stable liver cirrhosis and 34 patients (21 men and 13 women), aged 20–41 years, were diagnosed with chronic hepatitis C infection. The control group consisted of 25 healthy individuals (13 men and 12 women), aged 19–60 years. The serum concentration of F1+2 was determined by the immunoenzymatic assay Enzygnost F1+2 micro. There were no statistically significant differences observed in serum concentration of F1+2, both in patients with stable cirrhosis and with CHC, compared to controls. However, in 16.7% of patients with cirrhosis and in 35.3% of patients with CHC elevated serum levels of F1+2 were observed.

Stężenie fragmentu protrombiny 1+2 (F1+2) u pacjentów z marskością wątroby i u chorych z przewlekłym zapaleniem wątroby typu C

Celem pracy była ocena stężenia F 1+2 w surowicy krwi chorych z marskością wątroby w przebiegu zakażenia wirusem HCV oraz u pacjentów z przewlekłym zapaleniem wątroby typu C (pzw C). Badania przeprowadzono w grupie 52 chorych, w tym 18 (8 mężczyzn i 10 kobiet) w wieku od 19 do 59 lat z wyrównaną marskością wątroby i 34 z pzw C (21 mężczyzn i 13 kobiet) w wieku od 20 do 41 lat, leczonych w Klinice Chorób Zakaźnych AM w Lublinie. Grupa kontrolna obejmowała 25 osób zdrowych, w tym 13 mężczyzn i 12 kobiet w wieku od 19 do 60 lat. Stężenie F 1+2 oznaczano metodą immunoenzymatyczną Enzygnost F1+2 micro. Nie stwierdzono istotnie statystycznych różnic w stężeniu F1+2 w surowicy krwi zarówno u chorych z wyrównaną marskością wątroby, jak i z pzw C w porównaniu z wartościami uzyskanymi w grupie osób zdrowych. Jednakże u 16,7% chorych z marskością wątroby i u 35,3% pacjentów z pzw C obserwowano podwyższone wartości F1+2.