CLINICAL STUDY

Prognostic importance of the monitoring of selected parameters in liver cirrhosis

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Abstract

Aim of the study: **To evaluate the prognostic importance of hepatic encefalopathy and monitoring of transaminase, total and conjugated bilirubine, synthetic liver functions in hospitalized patients with liver cirrhosis.**

Patients and methods: **At the Intensive Metabolic Care Unit of 1st Department of Internal Medicine, we evaluated 150 patients (87 males, 63 females) with liver cirrhosis at average age: 52.51±7.99 years, Child–Pugh score: 11.34±2.99. 47 patients had died during hospitalization, 103 patients have improved. Student t-test was used for statistical analysis.**

Results: **The patients who expired had significantly higher serum levels of transaminase, total and conjugated bilirubin during the treatment and higher grade of hepatic encefalopathy. Synthetic liver functions were significantly decreased in the group of the expired patients. In patients who died during hospitalization was observed the tendency to increasing of total and conjugated bilirubine and to decreasing of synthehic liver functions.**

Conclusion: **Mortality rate of the hospitalized patients with liver cirrhosis depends on the degree of impairment of the liver functions and its potential improvement during hospitalization.** ***(Tab. 8, Ref. 24.)***

Key words: liver cirrhosis, hepatic encephalopathy, albumin, cholesterol, bilirubin, prognosis.

The prognosis in patients with liver cirrhosis depends on the etiology, progress of the disease and associated complications. There is a variety of clinical, biochemical and other parameters determinating the survival of patients.

Portosystemic (hepatic) encephalopathy is characterized by behavioral changes, altered physical and mental functions that are directly related to liver disease. Patients with liver cirrhosis often develop chronic hepatic encephalopathy which progresses to exacerbations of liver cirrhosis. The onset of portosystemic shunt can lead to the manifestation or exacerbation of portosystemic encephalopathy. There are 4 stages of hepatic encephalopathy and minimal (subclinical) encephalopathy, which are can be established by use of defined tests. Table 1 displays West Haven criteria for the establishment of the degree of portosystemic encephalopathy. Patients with the diagnosis of hepatic encephalopathy have often increased serum ammonia levels. In the diagnosis of hepatic encephalopathy, psychomotoric tests (frequency of flapping tremor, number connection test, subtraction of numbers), laboratory results and neurological examination (EEG, evoked potentials) can be used (7).

Serum transaminase levels (AST, ALT) are usually elevated in patients with deteriorated liver cirrhosis. There are 2 types of elevation of liver function tests. In active viral or autoimmune hepatitis, ALT/AST is usually >1.5. In alcoholic acute hepatitis or acute necrosis in hypoxic liver disease, ALT/AST is usually <0.5. Most of the patients with liver cirrhosis have elevated bilirubin and conjugated bilirubin levels. Bilirubin is a part of Child–Pugh score. Normal levels of bilirubin and liver function tests are rarely seen (19).

Liver failure leads to a decrease in the synthesis of proteins. The half-life of albumin is around 20 days. Therefore in fulminant liver failure, hypoalbuminemia cannot be present. However

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Tab. 1. Mental stage (West Haven criteria).

Stage 0	Normal
Stage 1	Mild personality changes, alterations of sleep rhythm, decreased attention, euphoria or depression, retarded of ability to perform mental tasks
Stage 2	Drowsiness, lethargy, inappropriate behaviour, intermittent loss of orientation (usually that in time)
Stage 3	Somnolent but rousable, disorientation (in time and/or place), loss of meaningful communication, incomprehensible speech, unable to perform mental tasks
Stage 4	Coma

Tab. 2. Diagnoses of patients with liver failure.

Diagnosis	No of patients
Alcoholic liver cirrhosis	99
Chronic hepatitis C with progression to cirrhosis	19
Chronic hepatitis B + C with progression to cirrhosis	2
Chronic hepatitis B with progression to cirrhosis	17
Primary biliary cirrhosis	3
Autoimmune hepatitis with progression to cirrhosis	7
Wilson's disease	3

the serum albumin level correlates well with the advancement of the disease. The serum albumin level is a part of Child–Pugh score. The half-life of cholinesterase is 8–10 days, prealbumin, transferrin and prothrombin are proteins synthetised mostly by the liver (15). Cholesterol is synthetised by liver, hypocholesterolemia occurs often in advanced cirrhosis (6).

Patients and methods

From January 1994 to June 1999, 171 patients with liver cirrhosis of Child–Pugh scores B and C were hospitalized at the Intensive Metabolic Care Unit of the 1st Department of Internal Medicine University Hospital in Kosice. Out of the latter, 150 patients (87 males, 63 females) were enrolled into the study. Patients with the diagnosis of liver cirrhosis, hepatocelular carcinoma or massive bleeding from oesophageal varices were excluded from the study. The average age of patients was 52.51±7.99 years, average Child–Pugh score was 11.34±2.99. 12 patients were diagnosed as being in grade B of Child–Pugh score, the rest of the patients as grade C. Patients' diagnoses are shown in Table 2.

After history and clinical examinations serum biochemistry was performed:

– AST (UV test, IFCC, Human, Germany),
– ALT (UV test, IFCC, Human, SRN),
– bilirubin (photometry, Lachema, Czech republic),
– conjugated bilirubin (photometry, Lachema, Czech republic),
– albumin (photometry, Human, Germany),
– cholinesterase (photometry, Human Germany),

Tab. 3. Group characteristics of patients with liver cirrhosis and liver failure.

	Group A	Group B	Statistical significance
Age (years)	53.21 ± 8.02	52.19 ± 7.73	NS
Child–Pugh score	11.83 ± 2.70	11.12 ± 3.23	NS

Tab. 4. Ammonia and portosystemic encephalopathy in patients with liver cirrhosis and liver failure.

Parameter	Group A	Group B	Statistical significance
Stage of hepatic encephalopathy	2.26 ± 0.71	1.71 ± 0.82	$p<0.01$
Ammonia (μmol/l)	131.03 ± 43.92	117.12 ± 41.07	NS

– cholesterol (enzyme method, Human, Germany),
– HDL cholesterol (precipitation reaction, enzyme method, Human Germany),
– ammonia (enzyme method, Biovendor, USA).

The degree of portosystemic encephalopathy was evaluated according to the mental stage by West Haven criteria (7).

In order to find out the prognostic importance of the selected parameters we divided patients into 2 groups:

– group A: patients who expired despite the treatment (47 patients),
– group B: patients who improved and were discharged, we evaluated only the first hospitalization (103 patients).

For statistical analysis, Student t-test for quantitative parameters was used. The groups were tested on the level 0.05 and 0.01 (17).

Patients' characteristics are shown in Table 3. There were no significant differences regarding the age or Child–Pugh score in both groups.

Results

Whereas serum ammonia levels of admission were not significantly different in both groups, clinical evaluation and mental status examination showed significantly higher degree of portosystemic encephalopathy in group A compared to group B ($p<0.01$). Results are shown in Table 4. The serum ammonia analysis was repeated only where clinically indicated, therefore repeated results were not statistically analysed.

Significantly higher serum ALT ($p<0.01$) and AST ($p<0.01$) levels were found in group A of patients compared to group B of patients at admission. During hospitalisation, both groups were found to increase repeatedly their levels of aminotransferases. The latter increase was higher in group A. Maximal serum AST ($p<0.01$) and ALT ($p<0.01$) levels were significantly higher in group A compared to group B. Results are shown in Table 5.

Tab. 5. Serum AST, ALT levels in liver cirrhosis patients with liver failure.

Parameter	Group A	Group B	Statistical significance
AST at admission (μkat/l)	6.22 ± 1.73	4.29 ± 1.82	p<0.016
AST: maximal level during treatment (μkat/l)	10.41 ± 4.93	5.03 ± 2.01	p<0.01
ALT at admission (μkat/l)	5.23 ± 1.94	3.77 ± 2.01	p<0.016
ALT: maximal level during treatment (μkat/l)	8.72 ± 4.11	4.23 ± 2.23	p<0.016

Tab. 6. Serum total and conjugated bilirubin in patients with liver cirrhosis and failure.

Parameter	Group A	Group B	Statistical significance
Bilirubin before therapy (μmol/l)	312.72 ± 104.30	141.20 ± 45.78	p<0.01
Bilirubin at the end of therapy (μmol/l)	341.79 ± 141.23	49.53 ± 18.12	p<0.01
Conjugated bilirubin before therapy(μmol/l)	263.81 ± 97.27	98.94 ± 47.25	p<0.01
Conjugated bilirubin at the end of therapy (μmol/l)	273.02 ± 117.10	29.54 ± 14.12	p<0.01

Tab. 7. Serum albumin and cholinesterase in patients with liver cirrhosis and failure.

Parameter	Group A	Group B	Statistical significance
Albumin before therapy (g/l)	24.18 ± 3.12	26.11 ± 5.03	p<0.05
Albumin at the end of therapy (g/l)	23.01 ± 4.70	28.93 ± 4.84	p<0.01
Cholinesterase before therapy (μkat/l)	20.04 ± 10.09	21.74 ± 11.03	NS
Cholinesterase at the end of therapy (μkat/l)	17.04 ± 9.21	22.11 ± 9.54	p<0.01

Tab. 8. Serum cholesterol and HDL cholesterol in liver cirrhosis and liver failure.

Parameter	Group A	Group B	Statistical significance
Cholesterol before therapy (mmol/l)	2.42 ± 1.33	2.81 ± 1.21	NS
Cholesterol at the end of therapy (mmol/l)	2.03 ± 1.21	2.83 ± 1.27	NS
HDL cholesterol before therapy (mmol/l)	0.39 ± 0.14	0.48 ± 0.17	p<0.010
HDL cholesterol at the end of therapy (mmol/l)	0.33 ± 0.13	0.46 ± 0.14	p<0.01

Patients in group A showed significantly higher serum bilirubin (p<0.01) and conjugated bilirubin (p<0.01) levels compared to group B of patients. Clinical improvement during hospitalization correlated with the decrease in serum bilirubin and conjugated bilirubin levels, compared to the increased levels of the expired patients. After the treatment, the levels of serum bilirubin (p<0.01) and conjugated bilirubin (p<0.01) were significantly higher in group A compared to group B, the fact of which is shown in Table 6.

Albumin and cholinesterase are synthetized by the liver. Therefore they reflect liver proteosynthesis. Serum albumin levels were significantly lower in group A (p<0.05) compared to group B at admission whereas serum cholinesterase levels were not significantly different. Serum albumin and cholinesterase levels increased in patients who had improved their clinical states during hospitalization. Serum albumin and cholinesterase levels had decreased in patients who expired. After the treatment, serum albumin (p<0.01) and cholinesterase (p<0.01) levels were significantly lower, in group A compared to group B, the fact of which is shown in Table 7.

There were no significant differences in serum cholesterol levels in group A and B before and after the treatment. Serum HDL cholesterol levels were significantly lower in the group A compared to group B before the treatment (p<0.01) and after the treatment (p<0.01). The results are shown in Table 8.

Discussion

Portosystemic encephalopathy is a common and serious complication in liver cirrhosis. It occurs frequently after shunt operations and transjugular intrahepatic portosystemic shunt in portal hypertension (11, 20). Gastrointestinal bleeding may lead to the development of portosystemic encephalopathy too (19). Portosystemic encephalopathy can occur in coincidence with bacterial infections, acute encephalopathy after spontaneous bacterial peritonitis; chronic portosystemic encephalopathy can develop after uroinfection (21). The stage of portosystemic encephalopathy is a part of Child and Child–Pugh classifications. It is an independent prognostic factor of liver cirrhosis. After the first manifestation of acute portosystemic encephalopathy, 1-year sur-

vival was experienced in 42 % of patients, 3-year survival in 23 % of patients (3). Hepatic coma developed in 17 patients, 10 patients have died, 7 patients have survived this complication. The degree of encephalopathy had been significantly higher in patients who expired compared to the survivors, whereas serum ammonia levels did not differ significantly between those groups.

Aminotransferase levels do not show typical characteristics, de Riitis coefficient is usually slightly elevated. In acute alcohol hepatitis the levels of AST/ALT are mostly >2 (19). In patients with alcoholic hepatitis, the elevation of ALT correlates well with survival; in patients with liver cirrhosis and alcohol hepatitis de Riitis coefficient correlates with survival (5). The elevation of aminotransferase levels in patients with liver cirrhosis can occur due to some other causes, namely like ischemic hepatitis or due to the activity of the underlying liver disease (12, 19). Significantly higher aminotranferases as well as maximal levels of aminotranferase had been observed at admission in the group of patients who expired compared to the group of patients who improved.

Increased serum bilirubin level correlates with the progression of liver cirrhosis and is a part of various prognostic schemes i.e. Child classification and Child–Pugh score. On some diseases as primary biliary cirrhosis icterus is the basic sign, whereas in others, as chronic hepatitis C and liver cirrhosis it does not have to be present even in advanced cases of the disease (19, 22). Elevated serum bilirubin levels occur more frequently in liver cirrhosis with ascites (16). Elevated serum bilirubin level is an independent prognostic factor in alcohol liver cirrhosis, alcohol hepatitis, during sclerotherapy after the first bleeding from oesophageal varices and in chronic viral hepatitis with liver cirrhosis (9, 10, 18). In three-month survival, it is not the Child–Pugh score but serum endotoxin and bilirubin levels that are of prognostic importance in patients suffering from liver cirrhosis (4). Serum bilirubin level can be used as a predictor of 1-year survival of liver cirrhosis patients (1). In our study, significantly higher serum bilirubin and conjugated bilirubin levels before and after the treatment were found in the group of expired patients compared to patients who clinically improved. An increase in the serum bilirubin level had been found in patients who expired, whereas a decrease in bilirubin was observed in the group of survivors.

In advanced liver cirrhosis, a decrease in proteosynthetic functions is present with low levels of serum albumin, cholinesterase and prothrombin. The serum albumin level is a part of Child–Pugh classification, albumin levels corelate with the Child–Turcotte score ($p=0.027$) (2). Low serum albumin levels are more common in vascular decompensation of liver cirrhosis (16). Serum albumin and cholinesterase levels are good prognostic factors of alcohol liver cirrhosis and together with the size of oesophageal varices they could create a prognostic index for survival in patients with the latter diagnosis (23). Serum cholinesterase level (however not that of albumin) is a good prognostic marker for long-term survival of patients with liver cirrhosis (1). In our study, serum albumin levels before and after the treatment were significantly lower in the group of expired patients compared with the clinically improved patients. Serum cholinesterase levels did not initially differ significantly, however we found significantly lower levels after the treatment in the group of expired patients compared to the patients who survived.

Cholesterol is synthetized by the liver. The synthesis decreases not only in total cholesterol but also in HDL and LDL cholesterol in the liver of patients with advanced liver cirrhosis (6). Serum cholesterol level is independent prognostic factor of compensated liver cirrhosis (24). D'Arienzo et al (1998) examined the importance of serum cholesterol level in patients with Child–Pugh C viral cirrhosis. All patients with serum cholesterol level less then 100 mg/dl have expired within 17 months, 75 % of other patients have survived for more than 2 years ($p<0.0001$) (8). Serum cholesterol correlates directly with cholinesterase levels and indirectly with bilirubin levels. Serum lipoprotein (a) level decreases depending on the grade of liver disease and it is advised to use it in the monitoring of liver functions (13). In our study, serum HDL levels were significantly lower in the group of non-survivors compared to survivors before and after the treatment. We point out to the fact that serum cholesterol levels may be increased in cholestasis, mainly in primary biliary cirrhosis. The treatment with ursodeoxycholic acid can be effective in these cases condition (14).

Patients with liver cirrhosis who have expired during the hospitalization atn the Intensive Metabolic Care Unit had had higher grade of portosystemic encephalopathy, higher levels of aminotransferases, serum bilirubin, conjugated bilirubin and lower levels of serum albumin, cholinesterase, cholesterol and HDL cholesterol compared to the survivors, the facts of which appeared to depend on the advanced stage of liver disease advancement in non-survivors.

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