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Blood Serotonin (5-HT) Level and 24 Hrs Urinary Excretion of 5-Hydroxyindoleacetic Acid (5-HIAA) in Patients with Active Liver Cirrhosis and in Patients with Hepatic Encephalopathy

Poziom serotoniny (5-HT) w surowicy krwi i ilość dobowego wydalania kwasu 5-hydroksyindolooctowego (5-HIOK) u chorych z marskością aktywną wątroby i u chorych z encefalopatią wątrobową

INTRODUCTION

The serotonin (5-HT) is a biogenic amine. It is a derivative of the L-tryptophan. The liver has a very important role in the formation and disintegration of this amine. The liver is the place of decarboxylation of 5-hydroxytryptophan to the serotonin under the influence of monoamino oxydasis to the 5-hydroxyindoleacetic acid. The clinical observation and the experiments of many scientists have shown the disorders in the metabolism of the serotonin and in the cirrhosis of the liver as well (2, 6, 7, 16). The clinical observations have proved that the hepatic encephalopathy is a very dangerous complication of the liver diseases. It causes the disorders of the intellectual function, it disorders the personality of the patients and gives many neurological symptoms. A lot of authors pay attention to the displacement in the aminoacid balance both in the serum and in the brain-spinal liquid in the pathogenesis of the hepatic encephalopathy. They also pay attention to the disorders between the checked and the stimulated neurotransmitters (3, 4, 10, 18, 19).

The serotonin in the correct brain's function is a very important factor whose precursor is the tryptophan. The serotonin is a mediator neurohormon in the chemical transmition of the impulses in the synapses and it models many functions in the brain (3, 4, 17).

These data made us start research of the 5-HT level in the serum of the blood and the quantity of its final metabolite 5-HIAA, which is evacuated with the urine, in patients with clinical symptoms of the hepatic encephalopathy in chronic liver diseases.

MATERIAL AND METHODS

Group I consists of 30 patients (10 women and 20 men), 18—27 years of age with active liver cirrhosis. Group II consists of 11 patients (4 women and 7 men), 27—68 years of age with the

symptoms of the hepatic encephalopathy in the chronic liver diseases (Table 1). All the patients were treated in the Department of the Gastroenterology in the Medical Academy in Lublin. The diagnosis was determined on the basis of clinical, biochemical and morphological criteria. There were 7 persons with the symptoms of the hepatic encephalopathy in the active liver cirrhosis post the inflammation of the liver and 4 persons with the clinical symptoms of the uncompensation of the function liver. The anamnesis has shown the chronic abuse of the alcohol.

The control group consists of 15 healthy persons 18—40 years of age. The serotonin was determined by the Ashcroft's et al. method (1). The 5-HIAA in the urine was determined by MacFarlane et al. method (9). The results were analysed by the statistical method and the essential differences between the average results were tested by the *t*-Student test.

Table 1. Groups of examined patients

Group	Number of cases	Sex		Age years
		males	females	
I	30	20	10	18—72
II	11	7	4	27—68

Group I — patients with *cirrhosis hepatis activa.*
Group II — hepatic encephalopathy in the group of patients with chronic hepatic pathology.

RESULTS

The average level of the 5-HT in the serum in the control group was 0.47 μg/ml (from 0.33 to 0.69 μg/ml). The average level of 5-HT in the serum of the patients with the active liver cirrhosis was 0.33 ± 0.15 μg/ml and was essentialy statistically lower than results in the control group ($p < 0.001$). The average level 5-HT in the serum of the patients from group II was $0.23 \pm \pm 0.05$ μg/ml and was essentialy statistically lower than the results in the control group ($p < 0.001$). It was also lower than the level of the 5-HT in the patients with the active liver cirrhosis without the symptoms of the hepatic encephalopathy ($p < 0.01$). These results are shown in Table 2 and in Fig. 1.

The 24 hrs urinary excretion of 5-hydroxyindoleacetic acid in the control group was from 5.58 to 10.1 mg (average 7.58 ± 1.34 mg). The 24 hrs urinary

Table 2. Comparison of the mean blood levels of 5-HT in μg/ml in the control group and in the groups of examined patients

Group	*n*	*x*	*SD*	Range	Statistical significance
control	15	0.47	0.1	0.33—0.69	
I	30	0.33	0.15	0.15—0.55	$p<0.001$
II	11	0.23	0.05	0.15—0.31	$p<0.001$

Explanation: *n* — number of estimations, *x* — mean, *SD* — standard deviation.

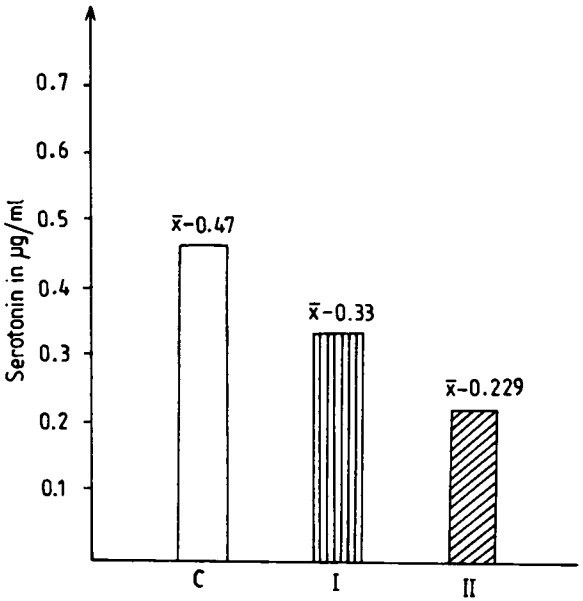

Fig. 1. Comparison of the mean blood levels of 5-HT in µg/ml in the groups: C — control, I — patients with *cirrhosis hepatis activa*, II — patients with hepatic encephalopathy; I/II — $p < 0.01$, C/I — $p < 0.001$

excretion of 5-HIAA in group I was 5.15 ± 1.46 mg) (from 1.3 to 10.0). It was statistically essentially lower in comparison with the average results of the control group ($p < 0.001$). In group II 24 hrs excretion of 5-HIAA was from 1.4 to 7.4 mg (average 4.13 ± 2.22). The difference between this excretion and the average result from the group I was statistically essentially lower ($p < 0.05$). These results of 24 hrs urinary excretion 5-HIAA are in Table 3 and in Fig. 2.

DISCUSSION

The medical research has shown that the 5-HT level in the serum of patients with active liver cirrhosis with the symptoms of hepatic encephalopathy in chronic liver diseases is lower that the results of the control group. At the same time there was a lower level of excretion of final metabolite of serotonin 5-HIAA in the urine/24 hrs in these patients.

The other authors also found the disorders in the metabolism of the serotonin (5, 7, 16). The experimental investigations are very important to explain this problem. Pentikainen et al. (13) while doing their investigations on the isolated, perfundated rat's liver proved that the cirrhotic liver uses much less serotonine which is served to the perfundate liquid than the good one. Kekki et al. (6) parallelly to determining the grade of escapement of the serotonin which

Table 3. Comparison of the mean urinary excretion of 5-HIAA in mg during 24 hrs in the control group and in the examined groups patients

Group	*n*	*x*	*SD*	Range	Statistical significance
control	15	7.58	1.34	5.58—10.1	
I	30	5.15	1.46	1.3—10	$p<0.001$
II	11	4.13	2.22	1.4—7.4	$p<0.05$

For explanation, see Table 2.

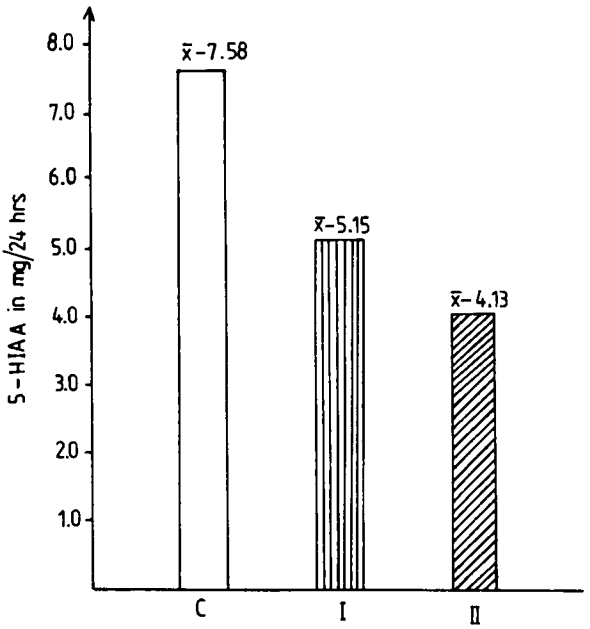

Fig. 2. Comparison of the mean urinary excretion of 5-HIAA in mg/24 hrs in the groups; for explanation see Fig. 1

was served to the portal vein or to the intestine investigated the evacuating of the metabolite of this substance to the bile. They found the decrease of the biliary evacuation of the free serotonin, but the higher evacuation of the serotonine connected with the glicuronic acid. A lot of authors pay attention to the increase of the contents of the tryptophan in the serum of the blood, which is the serotonine precursor, in the patients with liver cirrhosis (8, 12, 14, 15). Hirayama's (5) investigations have proved the different tolerance for the oral severing of L-tryptophan to the healthy and patients with cirrhotic liver. The patients with the cirrhotic liver complained about the somnolence and vertigoes. There were disorders in the moving and the clear neurological symptoms. At the same time they found the increase of 5-HT in the cerebro-spinal liquid. The

healthy patients did not have these symptoms or they were weak. These investigations have shown that the healthy liver protects the organism from the too big flow of the tryptophan to the brain.

These data suggest that the decrease of the level of the serotonin in the serum of the blood and the decrease of the 5-HIAA in the urine/24 hrs in the patients with liver cirrhosis may be the effect of neglecting the synthesis of this amine in the liver disease. It may also be the effect of quick creation of the connection of the serotonin with the glicuronic acid and their evacuation to the biliary tract. There may also be neglected the synthesis of the serotonin in the digestive system as the result of morphological changes of the mucosa in patients with liver cirrhosis.

The data concerning the level of the tryptophan and disorders of the synthesis and disintegration of the serotonin in the hepatic encephalopathy have the origins in the experimental researches (2, 6, 11). The authors pay attention to the increase of the free tryptophan in the serum of the blood which may penetrate through the cerebro-spinal barrier. The investigations of the tryptophan and the serotonin in the brain in the patients who died during *coma hepatica* have proved the increase of the contents of these substances in comparison with the patients with the acute hepatitis (16, 19).

Perhaps a very low level of 5-HT in the serum of the patients with the symptoms of the hepatic encephalopathy which have been proved in our investigation is caused by the quick penetrating of the free tryptophan to the brain-spinal liquid and the increased synthesis of 5-HT in the brain. According to many authors the high content of 5-HT in the brain is one of the pathogenic factors responsible for the clinical symptoms of the hepatic encephalopathy.

Conclusions

1. Blood serotonin (5-HT) level and 24 hrs urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) in patients with liver cirrhosis was decreased in comparison with the control group.
2. Blood serotonin level is essentially decreased in the patients with the hepatic encephalopathy in comparison with the control group, and the group of patients with liver cirrhosis without hepatic encephalopathy.
3. A special decrease of the level of the serotonin in the blood in patients with the symptoms of the hepatic encephalopathy may be one of the factors responsible for the symptoms from the brain.

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STRESZCZENIE

Badaniem objęto 30 chorych z marskością aktywną wątroby (grupa I) oraz 11 chorych z klinicznymi objawami encefalopatii wątrobowej w przebiegu przewlekłych schorzeń wątroby (grupa II). Grupę kontrolną stanowiło 15 zdrowych osób. W poszczególnych grupach wykonywano oznaczenia poziomu serotoniny (5-HT) w surowicy krwi oraz dobowe wydalanie kwasu 5-hydroksyindolooctowego (5-HIOK). U chorych grupy I stwierdzono statystycznie istotne obniżenie poziomu 5-HT we krwi oraz istotne zmniejszenie wydalania dobowego 5-HIOK w porównaniu z grupą kontrolną. U chorych grupy II poziom 5-HT we krwi był statystycznie istotnie obniżony zarówno w porównaniu z grupą kontrolną, jak i w porównaniu z grupą I.