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Acetylation Phenotype Impact on Early Postoperative Period in Viral Liver Cirrhosis

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ABSTRACT

Objective. The aim of our study was to identify some pathogenetic mechanisms and unify prediction factors for the development of complications after portosystemic shunting. Material and Methods: The present research involved 45 patients with liver cirrhosis complicated by portal hypertension. Buccal swabs and spot urine samples were used to determine acetylation phenotypes. The genotype of each individual was determined by polymerase chain reaction. High-performance liquid chromatography was used to determine acetylation phenotypes. Results: Rapid acetylation was revealed in 7 patients (15.6%) and slow acetylation was found in 38 patients (84.4%). In slow acetylation phenotype, a considerable progression of liver cirrhosis was observed in comparison with rapid acetylators alanin aminotransferaz (ALT) on 74.4 % in slow acetylation phenotype (SAcP) against 29.5 % in rapid acetylation phenotype (RAcP); total bilirubin on 111.8 % in comparison with 42%, respectively; the level of ammonia in blood was 247.8% compared to 62.5%). Recommendation: Taking into consideration the acetylation phenotype of liver cirrhosis patients can help in predicting possible side-effects and evaluate efficiency of drugs that are metabolized by N-acetylation.

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INTRODUCTION

Management of patients with liver cirrhosis complicated with portal hypertension after central portosystemic shunting. Hence, studying of acetylation polymorphism is currently relevant not only because many medical products are metabolized by acetylation reactions but also owing to better understanding the molecular basis of acetylation. These genetically caused metabolism variations of pharmaceuticals explain specific features of pharmacologic and therapeutic effect of drugs. Two genes found in humans are known to be responsible for activity of N-acetyl transferase. Recent research has shown that some alleles of these genes influence individual susceptibility to some diseases.

One of urgent problems in current pathologic physiology is studying the mechanisms of a disorder of detoxification functions of the liver in patients with various forms of liver pathology [1]. The hepatic endoplasmic network contains a family of isoenzymes of cytochrome P450 that is specific to various substrata. The processes of acetylation play an important part in interstitial metabolism. At present, acetylation phenotypes are considered to be a genetically determined ability of the body to metabolize compounds containing amino groups [2].

All pharmaceuticals pass the specific pharmacokinetic pathway by virtue of certain enzymes controlled genetically. Wide polymorphism in humans suggests that the fate of a pharmaceutical at any pharmacokinetic stage is associated with the polymorphic system of an enzyme or protein. It also causes diverse reactions of individuals to medicines [3].

To neutralize toxic products of metabolism or toxic substances in tissues some adaptable mechanisms, including those arranged in the toxigenic-kinetic, humoral, immunologic, and metabolic systems responsible for maintaining homeostasis in the body, have been developed in the course of evolution. Among them, the oxygen-dependent enzymes of the monooxygenase system play the important role [2]. Genetic differences in regulation, expression and activity of the genes, that code production of enzymes during the first and second

phases of xenobiotic biotransformation, can become a key factor of susceptibility to toxic effect of xenobiotics and development of a pathological process in the liver [4, 5].

Recently modern approaches of personalized medicine have been developed, e.g. assessment of the gene activity on the basis of studying the matrix RNA and drug metabolism [4]. Pharmacologic and kinetic research of pharmaceuticals is being conducted in many countries to evaluate the modes of drug dosing, considering individual variability of phenotypes of genetically determined biotransformation systems [5]. These studies will help not only to select the optimum doses of pharmaceuticals but to predict possible complications of the primary disease as well.

The aim of study was to identify some pathogenetic mechanisms and unify prediction factors for the development of complications after portosystemic shunting.

MATERIAL AND METHODS

Ethical approval

The review board and ethics committee of RSSPMCS named after acad. V.Vakhidov approved the study protocol and informed consents were taken from all the participants.

The results of examination of 45 patients with viral liver cirrhosis complicated by portal hypertension (PH) have been analyzed. Morphological examination revealed large-nodule liver cirrhosis (LNLC) in over half of them (26 patients; 57.8%); 19 patients (42.2 %) had small-nodule liver cirrhosis (SNLC). In 39 patients, cirrhotic transformations of the liver were caused by viral hepatitis B, and in 6 patients it developed after viral hepatitis C. At the time of examination, antibodies to HCV were found in all 6 patients, and 39 patients had positive HBs-Ag. The patients were examined before and after central portosystemic shunting (PSS) with spleen preservation and after selective distal splenic-renal anastomosis (DSRA). The clinical course after the surgery was severe in 3 (6.7 %) patients, rather satisfactory in 5 (11.1 %) and uneventful in 37 (82.2 %) patients.

In addition to standard tests, the examination included evaluation of the level of reopirin metabolites, namely 4-amino-antipirin (4AAP) and N-acetyl-4-amino-antipirina (N-ac-4AAP) in urine. The latter method is specific because 4-AAP discharged with urine is a direct product of N- demethylation performed with microsomal monooxygenase system, while N-ac-4AAP is a product of further acetylation. The acetylating ability of the body was assessed by the method of Prebsting-Gavrilova modified by Anilova and Tolkachevsky. It was interpreted as slow if it did not reach 50%, and rapid when it made 50 % and more.

Before the surgery, a considerable decrease in excretion of reopirin metabolites was observed in all patients under study. For instance, in the SNLC patients, the level of 4 AAP in daily urine specimen was 3.6 times below the controls, and the level of the same metabolites in the LNLC patients was 7.36 times lower. The SNLC patients had 3-times lower N-ac-4AAP level, and that one in LNLC patients was 5.74 times lower. Rapid acetylation was revealed in 7 (15.6 %) patients, while slow acetylation was found in 38 patients (84.4 %).

RESULTS AND DISCUSSION

According to our findings, slow acetylation prevailed in patients with morphological variants of liver cirrhosis. For instance, the slow acetylation phenotype (SAcP) was found in 38 of 45 liver cirrhosis patients (84.4 %), while 7 (15.6 %) patients had the rapid acetylation phenotype (RAcP).

The comparative analysis of the basic blood biochemical parameters of patients with various types of acetylation made before and during the postoperative period has shown that an increase in the basic biochemical indicators of the liver did not depend on the type of acetylation. However, the values of these indicators were different in the compared groups. For instance, if a cytolytic component manifested itself as an increase in the levels of ALT and aspartate aminotransferase (AST) in blood of the patients before the surgery was almost identical in both groups, the postoperative indicator in the group of patients with RAcP was a little lower, than in the ones with SAcP.

The basic biochemical tests of blood before and after the postoperative period in patients with various morphological forms of cirrhosis demonstrated aggravation of these indicators depending on the liver cirrhosis form. As Figure 1 shows, a more favorable liver cirrhosis course in patients with rapid acetylation is obvious. For instance, if the ALT level increased from 212.7±46.5 nmol\l to 383.4±127.2 nmol\l in slow acetylation (i.e. a gain made 74.4 %), in the rapid type, the gain appeared to be considerably smaller: 29.5 % ($P < 0.05$). After surgery the total bilirubin level in the blood of patients with SAcP increased from 25.4±6.7 to 53.8±19.7 mcmol/l that

made 111.8 %, while in the group with RAcP, hyperbilirubinemia was less expressed: before the surgery it was 23.1±4.2 32.8±8.1 mcmol/l or 42 % (P <0.01) and after it.

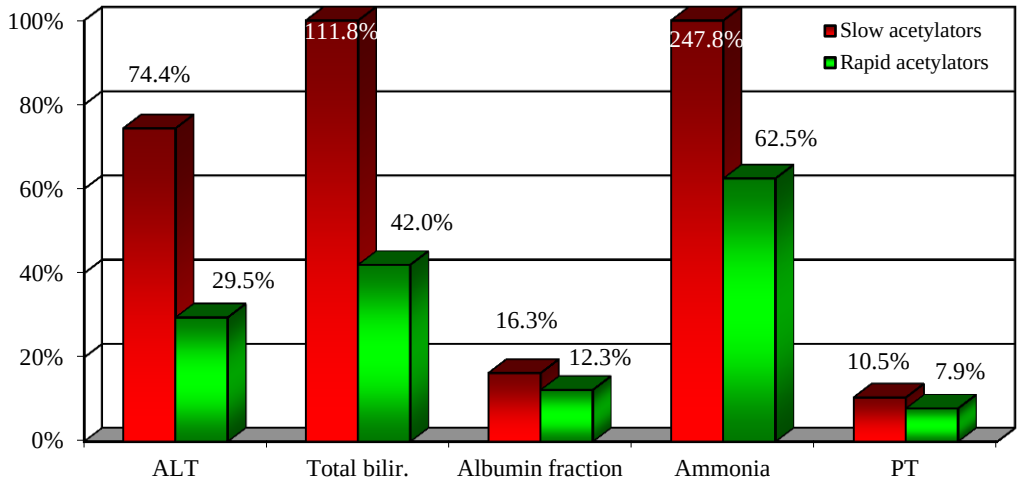

Figure 1. Progression of the basic biochemical indicators of blood depending on the acetylation type in early postoperative period

When analyzing the total protein levels, it was revealed that in the patients with slow acetylation, the albumin fraction before the surgery had been 39.2±2.9 g/L, while in the early postoperative period it had decreased to 32.8±3.9 g/L. The ammonia level in the blood of patients with cirrhosis is rather demonstrative. The indicator before the surgery and in early postoperative periods again demonstrates the advantage of rapid acetylation. For instance, in the patients with slow acetylation, the ammonia level increased by 247.8 %, while in the patients with the rapid one, it increased by 62.5 % (P<0.01).

The prothrombin time (PT) values before and after the surgery also differed, although to a lesser degree. In slow acetylation, PT decreased from 84.2±6.8 to 75.4±9.8, (i.e. by 10.5 %), and in the rapid type, a decrease appeared to be considerably smaller: 7.9 % (P <0.5).

Figure 2 presents the list and frequency of specific postoperative complications in the patients with different types of acetylation. The number of complications in patients with SAsP was observed to exceed the average incidence and specific complications developed more often than in rapid acetylators. Portosystemic encephalopathy was diagnosed in 6 patients and hepatic coma developed in 1 patient with SAcP, while in RAcP, only one patent had portosystemic encephalopathy of grades 1-2. Cholestasis was not observed in rapid acetylators, while in slow ones, it was observed in 2 cases. Edema and ascites developed in 7 patients with SAcP.

The correlation and comparative analysis demonstrated that parenhymatous-vascular decompensation in liver is characterized by: hepatic encephalopathy and mesenchimal and inflammatory response was observed in 36.8 % of patients with SAsP whereas in RAsP this complication developed only in one patient (14.3 %). No hemorrhage was observed in RAsP; in SAsP, it was found in 7.9 % of cases.

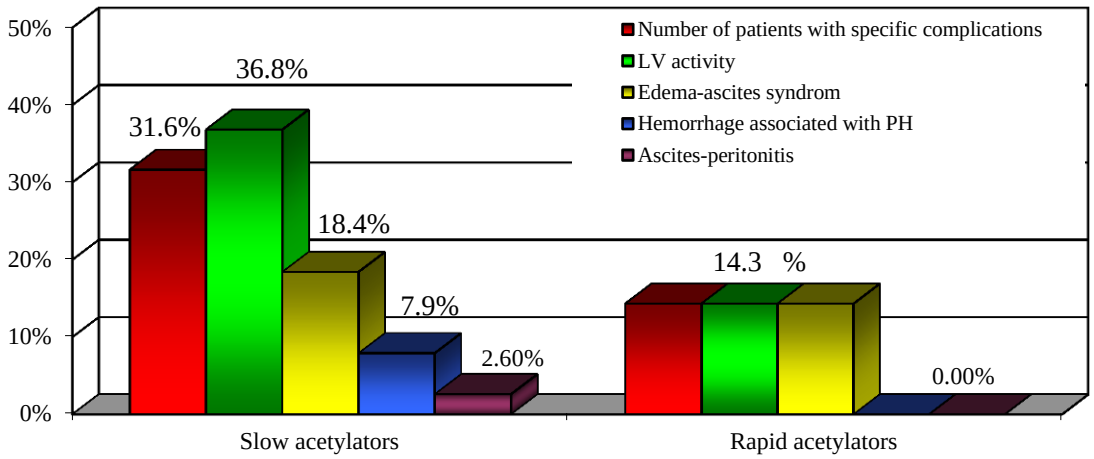

Figure 2. Progression of main biochemical indicators depending on the acetylation type

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CONCLUSION

Slow acetylation phenotype mainly develops in liver cirrhosis patients (84.4 %), it being characterized by more often specific and nonspecific complications in the postoperative period irrespectively of the morphological form of cirrhosis. In slow acetylation, considerable liver cirrhotic progression in comparison with rapid acetylators was observed (ALT on 74.4 % in SAcP, against 29.5 % in RAcP, total bilirubin on 111.8 % compared to 42 %, the level of ammonia in blood was 247.8 % against 62.5 %, etc.).

Therefore, acetylation phenotypes of all patients with liver cirrhosis should be determined in the preoperative period since those ones with slow acetylation are at risk of possible specific and nonspecific complications in the postoperative period. Taking into consideration the acetylation phenotype of liver cirrhosis patients can help in predicting possible side-effects and evaluate efficiency of drugs that are metabolized by N-acetylation.

DECLARATIONS

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Authors' Contributions
All authors contributed equally to this work.

Competing interests
The authors declare that they have no competing interests.

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