Актуальная Инфектология

УДК 616.36-002-085-036.8 *DOI: 10.22141/2312-413x.3.12.2016.81705*

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INCREASING EFFICACY OF TREATMENT IN PATIENTS WITH STEATOHEPATITIS

Summary. *This paper presents the results of a study of patients with nonalcoholic steatohepatitis, alcoholic steatohepatitis, and drug-induced liver injury. In patients with liver injury, changes in intestinal microflora were marked. After a combination therapy of this pathology with L-ornithine L-aspartate and symbiotic, an improvement of biochemical, clinical indicators was observed, as well as a decrease in fatty degeneration, reduction of elastographic indicators of liver fibrosis. The introduction of the drug formulation L-ornithine L-aspartate and symbiotic in the complex of conservative treatment of steatohepatitis help to prevent complications and increase the treatment efficacy of these diseases.*

Key words: *L-ornithine L-aspartate, Lactobacillus casei, Bifidobacterium longum, fructooligosaccharides, steatohepatitis, endotoxins.*

Introduction

Obesity and metabolic syndrome are increasing in the population, and so is nonalcoholic steatohepatitis. Continuous and recurrent course of hepatic diseases and their complications is accompanied by a progressive structural and functional damage of these organs and is accompanied by a significant decrease in quality of life that allows to consider these diseases in terms of an important medical and social problem and envisages the search for new directions of improving treatment and prevention of this pathology [7, 9, 10, 13].

The course of hepatic diseases is often accompanied by the damage to the intestinal microflora that contributes to the development of metabolic disorders and chronic intoxication. Excessive accumulation of free radicals and lipid peroxidation products is one of the leading pathogenetic mechanisms of hepatocellular lesions due to the damage to the lipid layer of cell membranes and metabolic disorders in the liver with the subsequent development of biliary insufficiency [1, 4, 6]. Bacterial overgrowth syndrome plays an important role in the development of hepatic steatosis [11]. Ammonia has been the most studied gut-derived neurotoxin, produced from the breakdown of proteins and amino acids. Ammonia is produced by the gastrointestinal tract in two ways: by direct ammonia liberation from breakdown products of dietary protein and metabolism of circulating glutamine (GLN) and by the gut microbiome acting upon urea and ingested food. Concentrations of ammonia are kept relatively constant in the blood by efficient detoxification processes, involving hepatic production of urea and synthesis of GLN from glutamate (GLU) by the action of glutamine synthetase (GS), which is located in the liver, muscle, and brain. Hyperammonemia is commonly seen in chronic liver disease, as are high levels of circulating endotoxins, as the liver fails to detoxify the portal circulation draining the intestines, which are heavily colonized by metabolically active bacteria, or else because the portal blood supply bypasses the liver through the development of a collateral circulation in the presence of portal hypertension. In addition, damage to the liver and the intestine can result from side effects of drugs: nonsteroidal anti-inflammatory glucocorticoids, salazopyrazins, statins, antihypertensives, etc. [2, 3, 13]. The practical importance of this paper consists in clarifying the mechanisms of progression of steatohepatitis, improving the efficacy of this pathology treatment with the use of a L-ornithine L-aspartate (LOLA) and symbiotic (prebiotic + probiotic). LOLA is a treatment directed at removal of circulating ammonia. Ornithine promotes hepatic removal of ammonia by stimulating residual hepatic urea cycle activity through action of ornithine carbamoyltransferase and carbamoylphosphate synthetase. Additionally, ornithine and aspartate are both substrates for the urea cycle. In perivenous hepatocytes, ornithine and aspartate combine with α-ketoglutarate to produce GLU. GLU is used by skeletal muscle and brain to use ammonia, via the action of glutamine GS to produce GLN, reducing the amount of circulating ammonia. Prebiotics are nondigestible food ingredients, stimulating growth of select colonic bacteria to improve host health, whereas probiotics are live microbial food supplement improving host gut microbial balance. Symbiotics are a combination of the two [5, 11].

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The study objective — evaluation of the treatment efficacy of steatohepatitis using Larnamin (L-ornithine L-aspartate) and Lactiale (*Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophylus, Bifidobacterium longum, Lactobacillus bulgaricus* (1,00 • 10^8 per capsule) with fructooligosaccharides).

Materials and Methods

Seventy-five patients with steatohepatitis have been examined in the gastroenterology department, including those with non-alcoholic steatohepatitis (NASH) — 33 (44 %), alcoholic steatohepatitis (ASH) — 24 (32 %), drug-induced liver injury (DILI) — 18 (24 %). For establishing accurate diagnosis of liver injury standard diagnostic criteria were used for NASH [5, 11], ASH [8] and DILI [4]. Seventy-eight percent of the patients had obesity, 37 % — type 2 diabetes. The body mass index varied from 17.8 to 33.7 kg/m^2. Among the examined patients, there were 64 % women and 36 % men aged 25 to 67 (mean age — 43.9 ± 8.4 years).

All patients, depending on the treatment, were assigned into 2 groups: in the experimental group, in addition to the basic therapy, Larnamin and Lactiale were administered (L&L treatment); the patients in the control group remained on basic treatment without L&L treatment. Each group was subdivided into three subgroups depending on the first-listed diagnosis (NASH, ASH, DILI). All analyzed subgroups were equivalent by diagnosis, age and sex. Basic therapy included the low animal fat diet (30–90 g/day) and with restriction of particularly rapidly digestible fats (150 mg/day). As a part of basic treatment, the patients received, behavioral therapy and adequate physical activity for 30 min/day.

According to the L&L treatment, the LOLA and symbiotic were administered for 3 months.

The diagnosis was verified on the basis of a complex of clinical laboratory studies (general clinical tests, intestinal endoscopy, coprogram and stool culture, fractional multi-moment duodenal intubation). To study the functional state of the liver, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGTP) activity, the levels of cholesterol, triglycerides, high-, low and very low density lipoproteins, total and direct bilirubin, blood total proteins, fasting glycemia and glycemia 2 hours after glucose challenge, blood pressure were studied; insulin resistance index was calculated. All patients underwent ultrasound investigation (apparatus Aixplorer®, Supersonic Imagine, France) with shear wave elastography, which allows to get objective information about the stiffness, elastic properties of the liver tissue during a routine real-time ultrasonic scan. The presence of hepatic fibrosis was determined by the propagation of elastic waves of 20–30 ultrasonic pulses followed by calculating the average values of the deformation pressure (in kPa) [12]. Patients with viral hepatic lesions (hepatitis B, C viral markers, Epstein-Barr virus, and cytomegalovirus), autoimmune hepatitis were not enrolled in the study. To exclude helminthic invasion, chlamydiosis, toxoplasmosis, enzyme immunoassay was used.

According to the principles of the Helsinki Declaration, all the patients were fully apprised of the subject matter of treatment and the drug properties. The Statistical processing was performed by means of the SPSS13 system.

Results and Their Discussion

Our findings indicates, that after treatment of liver injury in two experimental groups (standard treated and with addition of Larnamin and Lactiale) patients were diagnosed with the significantly decreased manifestation of syndromes that are presented in Table 1. However, under the L&L treatment the percentage of patients with diagnosed symptoms was extremely less (Table 1).

Under the influence of the treatment (Table 1), an amelioration of biochemical indicators, which characterize the condition of the liver, was showed. The frequency of significant changes was higher in the groups receiving L&L treatment as compared to those without them.

During the study of hepatic parenchymal elasticity in patients receiving L&L treatment, positive dynamics were noted. In patients with NASH after treatment, the indicators were 5.7 ± 0.8 kPa, which corresponds to F0-F1 stage of hepatic fibrosis, according to Metavir scale and is significantly lower than the indicators in the patients before treatment (6.7 ± 1.3 kPa, F1 according to Metavir scale) at $p < 0.001$. In patients with ASH, the indicators after treatment were 6.1 ± 0.8 kPa, which corresponds to F0-F1 stage of hepatic fibrosis, according to Metavir scale and is significantly lower than the indicators in the patients before treatment (7.8 ± 1.1 kPa F1 according to Metavir scale) at $p < 0.001$ and 5.7 ± 1.1 kPa in patients with DILI after treatment, which corresponds to F0-F1 stage of hepatic fibrosis according to Metavir scale and is significantly lower than the indicators in the patients before treatment (6.5 ± 1.1 kPa F1, according to Metavir scale) at $p < 0.001$.

After combination therapy with the use of Larnamine and Lactiale, in stool culture of 52 % of patients, the growth of bifidobacteria was noted, as well as the growth of lactobacteria in 67 % of patients; also a significant decrease in the number of Staphylococci, yeasts, *Bacteroides, Protei, Cytobacter, Klebsiellae* in 42 % of patients (Table 2). These results indicated greater potency of the L&L treatment for restoration of microflora in patients compared to standard scheme.

As our data show, L&L treatment should be included into treatment complexes in patients with steatohepatitis of different aetiology. The L&L treatment prevents further spread of pathologic microflora and accelerates recovery.

Conclusions

1. Under the influence of the drug formulation Larnamine and Lactiale, a normalization of the intestinal microflora is observed, which has a positive effect on the functioning of the liver and the intestines, as well as an improvement of biochemical indicators, which is evidence of the activation of membrane enzymes necessary for normalization of carbohydrate, fat and protein metabolism, reduction of manifestations of fatty degeneration; also, a decrease in the number of elastographic indicators of liver fibrosis is observed.

2. The use of Larnamine and Lactiale in combination therapy in patients with NASH, ASH, DILI contributes to enhancement of the anti-inflammatory, hepatoprotective effect and the normalization of the intestinal microflora.

Table 1. Dynamics of biochemical indicators after the L&L treatment of liver diseases

Indicators	Type of liver injury								
	NASH (n = 33)			ASH (n = 24)			DILI (n = 18)		
	Before treatment	After standard treatment	L&L treatment	Before treatment	After standard treatment	L&L treatment	Before treatment	After standard treatment	L&L treatment
Total bilirubin, μmol/l	18.7 ± 2.4*	17.0 ± 2.1*	12.00 ± 2.38*#	31.0 ± 2.8*	22.0 ± 2.7*	16.0 ± 2.4*#&	24.7 ± 2.4*	23.8 ± 2.3*	18.0 ± 2.5 *#&
Direct bilirubin, μmol/l	7.0 ± 0.4*	5.9 ± 0.7*	3.5 ± 0.6*#&	6.7 ± 0.3*	6.1 ± 0.4*#	3.8 ± 0.5*#&	7.0 ± 0.4*	6.5 ± 0.4*	3.4 ± 0.6 *#&
ALT, IU/l	45.0 ± 1.7*	39.0 ± 2.5*#	24.0 ± 2.4*#&	64.0 ± 2.3*	47.0 ± 2.9*#	22.0 ± 2.7*#&	84.0 ± 2.4*	56.0 ± 2.8*#	32.0 ± 2.4*#&
AST, IU/l	40.0 ± 2.1*	35.0 ± 2.8*#	22.0 ± 2.3*#&	72.0 ± 1.4*	54.0 ± 2.2*#	32.0 ± 2.9*#&	67.0 ± 3.2*	39.0 ± 3.4*#	34.0 ± 2.3*#&
GGTP, IU/l	37.8 ± 2.1*	29.0 ± 1.9*#	19.1 ± 2.4*#&	87.1 ± 2.7*	69.0 ± 2.6*#	27.6 ± 2.9*#&	53.8 ± 2.1*	30.1 ± 2.6*#	19.1 ± 2.4*#&
Cholesterol, μmol/l	7.1 ± 0.4*	6.7 ± 0.8*	5.4 ± 0.7*#&	6.4 ± 0.6*	5.9 ± 0.8*	4.9 ± 0.6*#&	6.1 ± 0.4*	5.7 ± 0.5*	5.4 ± 0.7*
Total proteins, g/l	55 ± 3*	56 ± 5*	60 ± 3*	59 ± 7*	60 ± 5*	62 ± 4	55 ± 3*	58 ± 4*	60 ± 3*

Notes: *— differences are significant as compared to indicators in healthy people ($p < 0.001$); # — differences are significant as compared to indicators in patients before treatment ($p < 0.05$); & — differences are significant as compared to patients standard treated ($p < 0.05$).

Table 2. The percentage of patients with altered intestinal microflora composition after the L&L treatment of liver diseases

Microflora indicators		Type of liver injury								
		NASH (n = 33)			ASH (n = 24)			DILI (n = 18)		
		Before treatment%	After standard treatment%	L&L treatment%	Before treatment%	After standard treatment%	L&L treatment%	Before treatment%	After standard treatment%	L&L treatment%
Bifidobacteria	> 10^7 CFU/g (norm)	17*	37*#	73#&	11*	12*	64*#&	19*	35*#	53*#&
	< 10^7 CFU/g (below normal)	67*	33*#	25#&	61*	68*	34*#*#&	57*	52*	38*#&
	Absent	16*	30*#	2&	28*	20*#	2#&	24*	13*#	9*#
Lactobacteria	> 10^7 CFU/g (norm)	6*	41*#	64&	18*	24*	68#&	14	47*#	76#&
	< 10^7 CFU/g (below normal)	52*	32*#	23&	71*	59*#	21#&	72*	39*#	24#&
	Absent	42*	27*#	13*&	11*	17*#	11*&	14*	14*	0#&
Pathogenic or opportunistic pathogenic microflora		72*	38*#	12&	63*	40*#	25*#&	71*	62*	15#&

Notes: * — differences are significant as compared to indicators in healthy people ($p < 0.001$); # — differences are significant as compared to indicators in patients before treatment ($p < 0.05$); & — differences are significant as compared to patients standard treated ($p < 0.05$).

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Received 29.08.16

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ПОВЫШЕНИЕ ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ У БОЛЬНЫХ СО СТЕАТОГЕПАТИТОМ

Резюме. В данной статье представлены результаты исследования больных с неалкогольным стеатогепатитом, алкогольным стеатогепатитом и лекарственным повреждением печени. У пациентов с поражением печени были отмечены изменения микрофлоры кишечника. После комбинированной терапии данной патологии с использованием L-орнитин-L-аспартата и симбиотика наблюдалось улучшение биохимических, клинических показателей, а также уменьшение жировой дистрофии, снижение эластографических показателей фиброза печени. Введение лекарственного препарата L-орнитин-L-аспартата и симбиотика в комплексе консервативного лечения стеатогепатита помогает предотвратить развитие осложнений и повысить эффективность лечения этих заболеваний.

Ключевые слова: L-орнитин-L-аспартат, *Lactobacillus casei*, *Bifidobacterium longum*, фруктоолигосахариды, стеатогепатит, эндотоксины.

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ПІДВИЩЕННЯ ЕФЕКТИВНОСТІ ЛІКУВАННЯ У ХВОРИХ ЗІ СТЕАТОГЕПАТИТОМ

Резюме. У цій статті представлено результати дослідження хворих із неалкогольним стеатогепатитом, алкогольним стеатогепатитом і лікарським пошкодженням печінки. У пацієнтів з ураженням печінки були відзначені зміни мікрофлори кишечника. Після комбінованої терапії цієї патології з використанням L-орнітин-L-аспартату і симбіотика спостерігалося поліпшення біохімічних, клінічних показників, а також зменшення жирової дистрофії, зниження еластографічних показників фіброзу печінки. Введення лікарського препарату L-орнітин-L-аспартату і симбіотика в комплексі консервативного лікування стеатогепатиту допомагає запобігти розвитку ускладнень і підвищити ефективність лікування цих захворювань.

Ключові слова: L-орнітин-L-аспартат, *Lactobacillus casei*, *Bifidobacterium longum*, фруктоолігосахариди, стеатогепатит, ендотоксини.