**SOME ASPECTS OF THE ALCOHOLIC LIVER DISEASE**

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*If you know alcoholism, then you know all the medicine*

Paraphrasing William Osler

**Key words:** alcoholic steatosis, steatohepatitis, cirrhosis of the liver, quality of life, alcoholism

History shows that the use of fermented beverages existed since the Neolithic period (nearly 10,000 BC), and, as a consequence, liver disease has been developing for the same time [23]. Alcohol is still being a main cause of liver disease worldwide. Liver disease associated with alcohol consumption flow through one of three options: fatty liver, alcoholic hepatitis with fibrosis and liver cirrhosis. Steatohepatitis, that occurs in patients intaking large amounts of alcohol, is usually reversible in abstinence and not necessarily predisposing to the formation of chronic liver disease upon further abstinence or moderation in alcohol intake. Acute alcoholic hepatitis, which can occur when a large amount of alcohol is consumed over a long period of time, can flow from an asymptomatic "biochemical" disorder to fulminant hepatic failure and death. Liver cirrhosis in the outcome of steatosis/steatohepatitis involves transformation of normal liver parenchyma to the degradation of collagen fibers becoming the basic liver "tissue", which leads to the clinical manifestations of portal hypertension and liver failure.

The prevalence of alcoholic liver disease (ALD) depends on many factors, including genetic (e.g., propensity for alcohol abuse, sex) and phenotypic (e.g., availability of alcohol, social accessibility and affordability of alcohol), so it is difficult to determine which of them are basic and primary ones. Overall, the risk of liver disease increases with the amount and duration of alcohol consumption [4, 13]. It is important to know that excessive drinking is not sufficient for the occurrence of ALD. According to B. F. Grant et al., only 1 of 5 alcoholics has alcoholic steatohepatitis (ASH), and 1 of 4 ― liver cirrhosis. Threshold daily consumption of 40 g of pure ethanol can cause ASH-type pathological changes, while consumption of over 80 g per day is associated with increasing severity of alcoholic hepatitis. There is a clear dose-response correlation between alcohol consumption and frequency of formation of alcoholic cirrhosis ― daily consumption of more than 60 g of pure ethanol in men and 20 g in women [11]. According to others, fatty liver develops in about 90% of people who daily take more than 60 g of pure ethanol [7], but the same fatty liver can form in people who do not take alcohol [14]. Uncomplicated fatty liver is usually asymptomatic and can be completely reversed by refusal of alcohol for about 4-6 weeks [18]. Nevertheless, some studies showed that the progression of fibrosis and cirrhosis occurs in 5-15% of patients despite the complete abstinence [12, 26].

Problem of alcohol abuse is very acute in our country. Epidemiological data and figures about this are often different in the literature, but they are only the tip of the iceberg called "ALD". As it is mentioned above, alcoholism forms in patients earlier and more often than ALD. Alcohol addiction is a complex biochemical "combination" of ethanol conversion in the central nervous system with the development of endorphins and dopamine in the final stage, which are "vital" for patients with alcoholism. These people in our society often face with various types of social censure, administrative and criminal penalties, but because of certain features of the disease are not perceived by society as seriously ill.

Alcoholism diagnostics is based on clinical examination and conduction of special tests, such as questionnaire CAGE [10], the test for identifying post- intoxicational alcohol syndrome, a list of physical signs of chronic alcohol intoxication ("LeGo Grid", 1976) in the modification of O. B. Zharkov, P. P. Ogurtsova, V. S. Moiseev et al.

Diagnosis of alcoholic hepatitis is also based on careful anamnesis acquisition, clinical examination, and laboratory and instrumental investigations. Clinical manifestations are scarce: heaviness in the right upper quadrant, bloating, nausea and diarrhea after eating fatty foods. Most of the patients have no complaints. The majority (over 70%) is observed to have hepatomegaly with a smooth surface. Icteritiousness and spleen enlargement are rarely found. Laboratory studies are characterized by increased de Ritis ratio ― the ratio of aspartate aminotransferase and alanine aminotransferase. Other general and non-specific laboratory abnormalities include anemia, leukocytosis, thrombocytopenia, hypoalbuminemia, hypergammaglobulinemia, hyperbilirubinemia, hyperammonemia and other metabolic disorders. Liver biopsy is sometimes needed for diagnosis. The most characteristic histological ALD manifestations are: fatty degeneration of hepatocytes, presence of Mallory bodies, neutrophilic infiltration and perivenular fibrosis [16]. Diagnosis is based on detection of ALD classic signs and symptoms of liver disease in patients with a significant history of alcohol consumption. Patients tend to underreport their alcohol consumption, but the survey of family members and close friends can provide a more accurate assessment of alcohol consumption. Thus, the clinical suspicion of alcoholic hepatitis can be imprecise in patients in up to 30 % of the cases [22].

We conducted a comparative analysis of clinical patients with ASH and non-alcoholic steatohepatitis (NASH), the control group consisted of people of similar age who did not have liver disease. Differences between the parameters of comparison were considered statistically different upon p≤0.05. Study was conducted in accordance with the Declaration of Helsinki of the World Medical Association (in 2000 version with explanations given on the WMA General Assembly, Tokyo, 2004), the rules of Good Clinical Practice of the International Conference on Harmonization (ICH GCP), the ethical principles set out in EU Directive 2001/20/EC and national requirements of the Russian legislation. Study protocol was approved by the Ethics Committee of Kemerovo State Medical Academy; review and approval of research met the requirements of national legislation. Each patient signed an "Informed consent" to participate in the research.

Diagnosis was confirmed by clinical, laboratory, instrumental methods, most patients had a liver biopsy. Statistically significant differences were found in the range of clinical parameters. The objectives of the study did not include alcoholism identification in patients, psychiatric consultations were not provided, but ALD was diagnosed on the basis of anamnesis according to the patients’ and their relatives’ words, as well as the objective clinical data. All examined were asked to fill a series of tests, which included the Nottingham Health Profile on assessment the quality of life of patients [2], the intensity of subjective ailments was assessed by Giessen Somatic Complaints Questionnaire, developed at the University of Giessen psychosomatic clinic [1].

To the researchers’ surprise, the indicators in terms of quality of life were the best in the patients with ASH, and results of Giessen questionnaire indicated the highest "pressure complaints" in the control group. Research results are presented in Table 1.

Table 1

**Results of the life quality indices according to the Nottingham Health Profile and Giessen Somatic Complaints Questionnaire**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Index** | **ASH** | **NASH** | **Control group** | **p** |
| **М** | **±SD** | **М** | **±SD** | **М** | **±SD** |
| Vitality | 5.60000 | 13.41702 | 32.16271 | 35.81925 | 10.40000 | 12.09617 | 0.0000004 |
| Pain | 9.67305 | 15.70354 | 19.89525 | 28.36756 | 8.27633 | 12.68954 | 0.0124304 |
| Emotional state | 12.08085 | 14.95820 | 12.32085 | 14.18457 | 13.37567 | 13.88680 | 0.920190 |
| Sleep | 28.52695 | 33.31003 | 35.33644 | 28.70661 | 19.19500 | 26.54171 | 0.059933 |
| Social isolation | 8.66542 | 13.13223 | 11.95441 | 18.88667 | 9.91533 | 17.41684 | 0.554153 |
| Physical activity | 7.53136 | 11.39543 | 15.10407 | 17.25977 | 11.66100 | 12.51378 | 0.0170905 |
| Total NHP score | 71.9251 | 62.2467 | 125.8500 | 118.6458 | 75.4307 | 61.0578 | 0.0025104 |
| Exhaustion | 3.627119 | 2.778602 | 5.779661 | 3.939490 | 7.300000 | 2.878577 | 0.0000041 |
| Stomach trouble | 5.237288 | 3.962492 | 6.016949 | 3.785141 | 4.366667 | 3.547542 | 0.149593 |
| Rheumatic pains | 5.96610 | 4.820810 | 8.06780 | 5.429372 | 10.03333 | 5.536608 | 0.0021871 |
| Heart trouble | 2.576271 | 2.877999 | 4.508475 | 3.887969 | 4.633333 | 3.809999 | 0.0043312 |
| Sum score of body complaints | 17.40678 | 12.20672 | 24.01695 | 15.44009 | 26.53333 | 12.66473 | 0.0044892 |

Note:

1 ― statistically significant differences (р<0,05) between all the groups;

2 ― statistically significant differences (р<0,05) between group 1 and groups 2, 3;

4 ― statistically significant differences (р<0,05) between group 2 and groups 1, 3;

5 ― statistically significant differences (р<0,05) between group 1 and group 2.

Research data indicate that patients with ASH feel satisfactorily, despite the clinical and laboratory changes. Therefore, we often see these patients for the first time at the stage of severe ALD complications ― ascites, bleeding from varices of the esophagus and the stomach or colon, hepatic encephalopathy, etc. Alcohol effect on the central nervous system is so insidious that, besides severe liver disease, patients don’t "notice" the suffering of the myocardium, kidneys, musculoskeletal and peripheral nervous systems, and other systems and organs. Another dose of ethanol- drink eliminates all manifestations of the alcoholism as a severe systemic disease, determining patient’s good mood and well-being. At the same time the disease progresses, liver lesion becomes heavier. ALD problem, as well as alcoholism, went beyond the medical circle long time ago. These patients should be treated not like criminals but as seriously ill persons who need both medical care, and serious social support.

What can we do for ASH patients?

Today, there are different techniques for the treatment of alcoholism and ALD, varying from psychotherapy to medication and surgery. Complete alcohol abstinence is a key stone of ALD treatment. Patients often can’t achieve complete and lasting alcohol abstinence unaided, so treatment aimed at combating chemical dependency seems appropriate; disulfiram [25], and high-efficient naltrexone and acamprosate (atsetimotaurin) [6, 9, 15, 17, 30] are successfully used now. Hospitalization is prescribed for patients with jaundice, encephalopathy, ascites, bleeding, fever and other serious complications. Almost all the patients with alcoholic hepatitis have different degrees of malnutrition, but trophic disorders severity assessment remains a challenge, because there are no highly sensitive and specific clinical or laboratory parameters for these patients. They are often identified to have vitamins and minerals deficiencies, including vitamins A, D, thiamine, folic acid, pyridoxine, zinc and some others [20]. Degree of malnutrition in these patients directly determines the short-term (1 month) and long-term (1 year) mortality. During 1 year, 14% mortality after diagnosing the alcoholic hepatitis was recorded in patients with mild malnutrition as compared to 76% mortality in patients with severe malnutrition [32]. Enteral nutrition is more preferable for such patients than parenteral one, and the amount of protein in the diet should provide a positive nitrogen balance [22, 29 , 32].

 The use of corticosteroids as a specific therapy for alcoholic hepatitis is of great interest among hepatologists around the world. Three randomized controlled studies, evaluating the use of corticosteroids (prednisone 40 mg per day or its equivalent methylprednisolone 28 mg per day for 28 days) in patients with severe acute alcoholic hepatitis, indicate a significant increase in the immediate survival of these patients [19, 28]. Results of other randomized controlled trials were contradictory [8, 31]. Modern practical recommendations support the use of corticosteroids in patients with severe alcoholic hepatitis upon clear diagnosis [22]. However, the effectiveness of corticosteroids was not evaluated in patients with renal failure, active infection, pancreatitis, gastrointestinal bleeding, and some other severe complications.

Dysregulation of cytokines, including tumor necrosis factor (TNF) and some others, plays a key role in ASH pathophysiology. Pentoxifylline is the most studied in the anticytokine drugs group in ALD, which is an inhibitor of TNF synthesis. Elevated TNF levels were associated with higher mortality from alcoholic hepatitis. Several randomized, double-blind controlled studies on the use of pentoxifylline in alcoholic hepatitis had a significant reduction in mortality [1, 24].

ASH, particularly acute one, is the second most common indication for liver transplantation after chronic liver disease in several countries in Europe, North America, etc. [5, 21]. A very small number of such operations are performed in Russia today. Domestic gastroenterologists, physicians, resuscitators facing the need for effective ALD therapy are "armed" with the drugs of different mechanisms of action, which are combined into a group of "hepatic protectors". These drugs include ademetionine, ursodeoxycholic acid, ornithine aspartate, silymarin, ɑ-lipoic acid, and some others.

**Conclusion.** As it is emphasized in the most recent international guidelines, health care providers should be alert to the signs of the patient’s hidden alcohol abuse [22]. Many patients often deny alcohol intake. Furthermore, there are no clinical or laboratory ALD-specific signs. Alcohol addiction is determined by the patient’s physical tolerance and abstinence symptoms. It is very convenient to use a screening CAGE questionnaire:

**С ― Have you ever felt you needed to Cut down on your drinking?**

**А ― Have people Annoyed you by criticizing your drinking?**

**G ― Have you ever felt Guilty about drinking?**

**Е ― Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?**

 It is the preferred screening tool, with more than two positive responses, it has a 71%sensitivity and 95% specificity for alcohol addiction [3]. All the modern methods of influencing the patient must be used upon ALD identifying in order to maximally preserve his/her health, despite the non-standard course of this debilitating disease.

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Article is devoted to the alcoholic liver disease, which is being developed according to the type of steatosis/steatohepatitis/fibrosis, followed by its transformation into cirrhosis of the liver. Pathogenetic mechanisms of alcoholic liver lesion by the type of steatosis/steatohepatitis are described. Current data on the use of drugs with a high level of evidence and recommendations in the treatment of alcoholic steatohepatitis are represented. Article also provides our own research on the quality of life and the pressure of somatic symptoms in patients with different types of fatty liver disease.