Clinical and laboratory findings in patients with alcoholic hepatic disease

-ABSTRACT-

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Key words

• Acute alcoholic hepatitis
• Alcoholic steathosis
• Cirrhosis
• Alcohol
State of Knowledge

Alcohol, under different forms, concentrations, tastes, but with the same sort of effects is the most used drug in the entire world, having the advantage of legality and furthermore the acceptance without reluctance of the society. Alcoholism is recognized as a major problem, yet not the most important problem that modern society confronts with.

Among somatic diseases caused by chronic alcoholic intoxication, the forefront is occupied by digestive ones, mainly hepatopathy and alcoholic pancreatitis, of which cirrhosis clearly stands out, representing, we may say, the prototype of the damaging effect of alcohol on the organism. The numerous performed researches attested the existence of a correlation between regular alcohol consumption and liver diseases incidence. In Europe, alcohol is considered the most frequent cause of hepatic cirrhosis (50 – 70%). In the context of liver diseases, hepatic alcoholic disease, if we refer to its spreading and social consequences, it occupies the second place after viral etiology diseases. It is estimated that about half of the global cirrhosis mortality is assigned to excessive alcohol consumption.

Epidemiological studies proved the existence of a positive correlation between alcohol consumption per capita and cirrhosis mortality. In the countries where the annual per capita alcohol consumption overcomes 10 litres of pure alcohol, annual cirrhosis mortality varies between 20-30 and 100.000 inhabitants. The alcohol consumption index for Europe is 9.8 l/man/year.

In Romania, the alcohol consumption is constant, being represented by 7.7 l/man/year with a cirrhosis mortality between 20 to 100.000 inhabitants.

Alcohol is admitted to be normal and even healthy between certain limits, the favourable effects of moderate consumption on the cardiovascular system being widely accepted. It is a highly individual problem from what level it becomes pathological. At quantities that determine concentrations of 3.1-5.6 g/l, alcohol is regularly fatal.

The abuse is defined as the abnormal behaviour concerning alcohol consumption.

The alcoholism has gravity steps, but this term should be used only when dependence exists. Dependence can be: physical (characterized by alcohol tolerance growth, increasing amounts being necessary to obtain the desired effects and also by withdrawal syndrome that appears when interrupting alcohol consumption, requiring alcohol or sedatives for remission); psychological (characterized by the urge of permanently or
intermittent drinking, loss of self control, behavior problems, being unable to stop drinking after “tasting”, on any occasion).

Another modality of presenting alcoholism is in four steps: tolerance, psychological dependence, loss of self control and addiction.

A classification in types divides alcoholism in: alpha type – conflictual situations related alcohol consumption, associated with a certain degree of psychological dependence; beta type – occasional or periodical alcohol consumption, with no psychological dependence; gamma type – alcohol consumption associated with psychological dependence, loss of self control and, possibly, physical dependence; delta type – daily alcohol consumption, permanently, with the impossibility of stopping for 24 hours, without loss of self control, but associated with physical dependence and epsilon type – excessive periodical alcohol consumption, with loss of self control.

Excessively consumed alcohol has multiple damaging effects on the organism (besides the hepatic ones) of which we mention: the increased risk of esophageal cancer, parotiditis, gastro-esophageal reflux disease, acute and chronic pancreatitis (20 times more frequent at alcoholics), dilated cardiomyopathy, hypertension, cerebral infarction, cerebral disorders (Korsakoff dementia), psychological diseases, sensory-motor polyneuropathy, immune system alterations, malnutrition etc. Alcoholics life expectancy is 10-12 years less than in the general population.

The damaging effect of alcohol on the liver is proved by wide epidemiological studies. The classic examples that are used in order to demonstrate the relation between alcohol consumption and hepatic cirrhosis are the following: in France, standard country for alcohol consumption, the period of its decrease during the Second World War was associated with a decrease in the hepatic cirrhosis mortality, and its increase between 1946 and 1955 was followed by an increase in liver cirrhosis mortality. The continuous decrease in the alcohol consumption in France after 1966 resulted in decreasing mortality from cirrhosis, that in 1992 reached half of the rate it had in 1967 (16/100.000 versus 36/100.000 inhabitants). Similar data were also obtained in other European countries with high alcohol consumption, that presented large temporal variation (prohibition periods) and resulted in concordant modifications of cirrhosis mortality.

The risk of severe hepatic disease increases along with the quantity and the duration of alcohol consumption. For men, the risk of cirrhosis increases 6 times for an alcohol consumption of 40-60 g/day and 14 times for 60-80 g/day, in comparison with the risk present at a
consumption of 20 g/day. The only average accepted dose for producing hepatic cirrhosis is 160-180 g/day for 8-25 years. Less than 5 years alcohol consumption, even in extremely large doses, does not determine hepatic cirrhosis. However, disease risk significantly increases at over 80 g/day dose for more than 5 years. For women, increased risk dose for hepatic cirrhosis are significantly lower. It is worth pointing out that no study has shown the influence of the type of consumed drink, but only of the ethanol quantity (10 g of alcohol = 30 ml of whisky = 100 ml of wine = 250 ml of beer). Another important issue is the fact that those who drink every day are more affected than those who drink with intermittences and allow the organism to recover. As a general rule, people should be advised that at least two days a week not to consume any alcohol.

The drinker who develops cirrhosis most frequently is type gamma, who has only a variable degree of dependence and tolerates huge amounts of alcohol on extremely long periods of time.

All data indicate the fact that only a minority of the consumers develop a progressive liver disease, which suggests the existence of other risk factors.
Material and method

We performed a prospective study for 166 patients with hepatic ethanolic pathology hospitalized in the Medical Clinic I - Gastroenterology during 01.01.2006 - 01.03.2010. The patients were selected on the basis of a study protocol that included anamnestic data (study questionnaire), objective clinical data and paraclinical explorations.

The anamnesis included:

- Age, sex, location – important data for establishing the demographic characteristics of the group we studied;
- The presence of a history of digestive disorders. Therefore, we noted the history of hepatic alcoholic disease, regardless of clinical form (steatosis, alcoholic hepatitis or alcoholic cirrhosis), the history of viral hepatitis, drug consumption with toxic potential for the liver or industrial toxic with liver disease potential;
- Chronic alcohol consumption, also trying to evaluate daily amount and duration of alcohol consumption;
- Presence at the beginning of the hospitalization of the hepatic disease symptoms: jaundice, physical fatigue, manifestations belonging to the bleeding syndrome, the occurrence of ascites, edema, signs and symptoms of hepatic encephalopathy;
- Objective clinical assessment noted: the presence of jaundice, the bruises or epistaxis, gum bleeding, vascular stars in the superior vena cava territory, ascites, edema, neurological signs characteristic for hepatic encephalopathy;
- Biological assessment involved: changes in blood count (hemoglobin, leukocyte count or platelets count), glycemia levels, urea, creatinine, ALAT (GPT), ASAT (GOT), bilirubin, alkaline phosphatase, gamma-glutamyl-transpeptidase, prothrombin index, total cholesterol, lipemia;
- Ultrasound examination aimed dimensions, structure and echogenicity of the liver, portal vein caliber at the hilum, the splenic vein, spleen dimensions, the presence of ascites;
- Endoscopic evaluation aimed to find esophageal and gastric varices, as well as portal hypertensive gastropathy.

In numerous cases of alcoholic liver disease, major lesions (steatosis, hepatitis and hepatic cirrhosis) are associated and the definite diagnosis would require certain pathological examination to define their presence. Since in the vast majority of cases the performance of liver
biopsy does not change therapeutical decisions, we used a combination between laboratory examination, endoscopic and ultrasound criteria to differentiate alcoholic liver disease forms.

In order to assess the state of chronic alcoholic intoxication, questionnaire CAGE was used, being one of the best known and approved tests to be known for detecting hidden alcohol consumption, having a major informational potential. It can be widely used, being very accessible to patients. CAGE questionnaire includes the following questions:

1. Have you felt the need to put an end (Cut) to the alcohol consumption?
2. Are you bothered (Annoyed) by de suggestion that you have a problem with alcohol?
3. Do you feel culpable (Guilty) because of the excess of alcohol?
4. Do you have to consume alcohol in the morning to be able to wake up? (Eye opener)

CAGE Score is attained by marking 1 point for each affirmative answer; the presence of two or more affirmative answers suggest the presence of alcohol-related problems to the patient. If the patient did not answer with honesty to CAGE questions, the presence of alcoholic intoxication was checked by assessing alcoholic post-intoxication syndrome (APS), estate that occurs upon awakening after alcohol abuse. The gravity of post-alcoholic intoxication estates correlates with the gravity of chronic alcoholic intoxication. More than 15 affirmative answers in this survey represent a result with high probability of systematic and long-term alcohol consumption in dangerous to health quantities - loss of amount control occurs, disorder of the liver basal metabolism with acetaldehyde overproduction, abstinence and alcoholic post-intoxication states.

The evaluation of liver disease was performed by laboratory research that reflect the basic liver pathological syndromes.

Cytolysis syndrome was evaluated by determining transaminases values: ALAT (alanine aminotransferase) and ASAT (aspartate aminotransferase), using standard tests in accordance with IFCC (International Federation of Clinical Chemistry and Laboratory Medicine).

In order to determine cholestasis syndrome, the level of bilirubin, alkaline phosphatase (standard photometric test), total cholesterol, high density lipoproteins (HDL) and low density lipoproteins (LDL) (W.Friedewald precipitation method), beta-lipoproteinse (M.Burshtein turbidimetric method), triglycerides (enzymatic photometric method).
To assess hepatocellular insufficiency syndrome, total proteins were determined (unified Biuret method), serum albumin (colorimetric method with bromcresol), transferrin (immunoturbidimetric method), prothrombin index according to Quick method.

The investigation of immune-inflammatory syndrome included performance of the following tests: examination of humoral immunity parameters - Ig A, IgM, IgG (radial gel immunodiffusion method), the level of circulating immune complexes (CIC) by precipitation method with polyethylene glycol solution (Grivenici method) and cellular – total T-lymphocytes by spontaneous rosette method and their subpopulations: active T lymphocytes, T teophylline sensible and T teophylline resistant by teophylline rosette method.

Markers indicating alcohol consumption were also determined:: gamma glutamyl transpeptidase (γGT), glutamate dehydrogenase (GDH), alcohol dehydrogenase (ADH), serum alcohol level and carbodeficient transferrin (CDT).

γGT value was determined by photometric method proposed by Szas G. Glutamate dehydrogenase concentration and alcohol level were determined by standard tests. Alcohol dehydrogenase activity was determined by the method proposed by Gudamac. Determination of carbohydrate deficient transferring was performed by precipitation method of (desializate?) glycotransferrin of total transferrin, which was assessed by immunoturbidimetric method. Viral hepatitis markers were detected using immunoenzymatic-ELISA analysis method.

Liver functional status survey was completed by performing abdominal ultrasonography to determine the echogenicity of the liver parenchyma and the size of the liver, spleen and Doppler ultrasound, with the assessment of portal vein size and splenic vein. In some cases, it was also performed liver biopsy with anatomo-pathological examination. To elucidate concomitant pathology and hepatic disease complications further investigations were performed upper gastrointestinal endoscopy, colonoscopy, echoendoscopy (EUS).
Conclusion

1. Hepatic alcoholic disease was more frequent in males, due to a higher prevalence of chronic alcoholism in males. The most affected groups of age were those between 40 and 60 years. In terms of environmental origin, patients living in urban and rural areas were similarly affected.

2. Studying the amount and duration of alcohol consumption to the patients included in the study, we observed that the largest quantity of pure alcohol daily consumed by patients with hepatic cirrhosis was 68.8 g/day, and the longest duration of alcohol consumption was approximately 23 years. In all the groups studied was established that for producing an alcoholic hepatopathy, the dosis as well as the duration of alcohol consumption are lower for women than for men.

3. In the clinical presentation of the patients with chronic ethanolic intoxication prevailed hepatomegaly, jaundice and portal hypertension signs. Hepatomegaly was confirmed clinically and by ultrasound, liver dimensions at patients with alcoholic liver disease being significantly higher than the control group. Thus, hepatomegaly was identified as the most constant and often the unique sign at patients with alcoholic liver disease.

4. From the point of view of laboratory determined constants, anemia was present in a relatively low percent of patients, the its mechanisms being, however, varied. Trombocytopenia was diagnosed in 70% of the cirrhotic patients and leukocytosis was found in most patients with alcoholic hepatitis. Serum aminotransferases were elevated especially in patients with alcoholic hepatitis, forms with highly elevated valyes were scarcely present in the studied group. Bilirubin serum value was elevated to the majority of the patients with both alcoholic hepatitis and liver cirrhosis, cholestatic forms of disease being also diagnosed. The latter had generally a worse prognosis in comparison with cholestatic disease forms.

5. In the present study we had an increased level of HDL, triglycerides and β-lipoproteins at patients with alcoholic hepatitis, unlike the values published for viral hepatitis. No significant difference was present concerning HDL and β-
lipoproteins levels at patients with alcoholic liver cirrhosis. Only an increasing trend was observed in the level of triglycerides and cholesterol in patients with alcoholic cirrhosis.

6. Analyzing data about immunity of the patients included in the study, important changes were present in both the immune humoral system as well as in the cellular one. Testing humoral immunity index in patients with alcoholic hepatitis revealed the marked increase in Ig A in contrast with the viral forms in which Ig G is significantly elevated. Regarding serum Ig M and globulins, their values were elevated in all groups of patients studied compared with healthy subjects, but no differences in these indices were determined between the groups.

7. The evaluation of markers that indicate chronic ethanol consumption in patients with alcoholic liver disease reveals significant changes that may contribute to the establishment of a diagnostic algorithm of alcoholic liver pathology. Thus, in both acute hepatitis and liver pathology of alcoholic etiology, significant increases of γ-GT, carbohydrate deficient transferring and glutamate dehydrogenase were found.

8. Patients with acute alcoholic hepatitis have favourable evolution (in 78.26% of cases) under hepatoprotective treatment, vital support in severe forms and restriction of alcohol consumption. 5 deaths have been recorded in the group of 23 patients included in the study. The liver cirrhosis forms evolved with portal parenchymal decompensation depending on the stage of evolution of liver damage and on hygienic-dietary regime compliance.
EUROPEAN CURRICULUM VITAE FORMAT

PERSONAL INFORMATION

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Nationality  Romanian
Date of birth  September 24 th , 1949
Marital status  married

WORK EXPERIENCE

- Dates (from – to)  2000 - on-going
- Name and address of employer  Private Office in Family Medicine – CMI Dr. Constantin Muşetescu, Craiova, Romania
- Type of business or sector  Family Medicine
- Occupation or position held  Specialist in Family Medicine
- Main activities and responsibilities  Seeing out-centered patients, ambulatory healthcare

- Dates (from – to)  1992 – on-going
- Name and address of employer  “Christiana” Nursing College, Craiova, Romania
- Type of business or sector  Post-highschool studies
- Occupation or position held  Director
- Main activities and responsibilities  Managerial responsibilities

- Dates (from – to)  1990 - 1998
- Name and address of employer  State Nursing College, Craiova, Romania
- Type of business or sector  Post-highschool studies
- Occupation or position held  Director
- Main activities and responsibilities  Managerial responsibilities

- Dates (from – to)  1986 - 2000
- Name and address of employer  RAT, Craiova
- Type of business or sector  RAT Ambulatory Healthcare Center, Craiova
• Occupation or position held: General Practitioner
• Main activities and responsibilities: Ambulatory healthcare

• Dates (from – to): 1978 - 1986
• Name and address of employer: IJGCL Craiova
• Type of business or sector: IJGCL Ambulatory Healthcare Center, Craiova
• Occupation or position held: General Practitioner
• Main activities and responsibilities: Ambulatory healthcare

• Dates (from – to): 1976 - 1978
• Name and address of employer: Rural Ambulatory Healthcare Units of Danciulești, Goești, Danești
• Type of business or sector: Ambulatory Healthcare Units
• Occupation or position held: General Practitioner
• Main activities and responsibilities: Ambulatory healthcare

**EDUCATION AND TRAINING**

• Dates (from – to): June 09th, 2010 Craiova
• Name and type of organisation providing education and training: The National Society of Gastroenterology, Hepatology and Digestive Endoscopy, GASTRO 2010
• Principal subjects/occupational skills covered: Digestive Oncologic Pathology Course

• Dates (from – to): May 10th - June 10th, 2009 Craiova
• Name and type of organisation providing education and training: University of Medicine and Pharmacy Craiova
• Principal subjects/occupational skills covered: Alkaloids of Pharmaceutical Relevance in Clinical Practice

• Dates (from – to): April 12th – 13th, 2007, Timisoara
• Name and type of organisation providing education and training: ISHNE
• Principal subjects/occupational skills covered: International Workshop on the Risk Stratification in Patients with Ischemic Heart Disease

• Dates (from – to): July 13th–July 14th, Craiova
• Name and type of organisation providing education and training: Ministry of Health
• Principal subjects/occupational skills covered: Management of Type 2 Diabetes – National Education Programme for Family Doctors

• Dates (from – to): November 25th, 2006, Craiova
• Name and type of organisation providing education and training: Romanian National Society for the Study of Pain
• Principal subjects/occupational skills covered: Pain Management Course
• Dates (from – to)  October 14th–16th, 2004, Prahova
• Name and type of organisation providing education and training
  AMA, National Society of Internal Medicine, National Society of Cardiology
• Principal subjects/occupational skills covered
  Advances in Diagnosis and Treatment of Microvascular Syndromes

• Dates (from – to)  October 28th–29th, 2005, Bucharest
• Name and type of organisation providing education and training
  Romanian Association for the Study of Liver
• Principal subjects/occupational skills covered
  XVth National Congress of Hepatology

• Dates (from – to)  October 4th, 2005, Craiova
• Name and type of organisation providing education and training
  University of Medicine and Pharmacy Craiova
• Principal subjects/occupational skills covered
  Up to date in Diagnosis and Treatment of Chronic Infection with B Hepatitis Virus

• Dates (from – to)  November 2nd, 2003, Craiova
• Name and type of organisation providing education and training
  University of Medicine and Pharmacy Craiova
• Principal subjects/occupational skills covered
  Up to Date in Hepato-Bilio-Pancreatic Ultrasound

• Dates (from – to)  November 24th, 2002, Craiova
• Name and type of organisation providing education and training
  University of Medicine and Pharmacy Craiova
• Principal subjects/occupational skills covered
  Up to Date in Gastroenterology

• Dates (from – to)  1997, Craiova
• Name and type of organisation providing education and training
  University of Medicine and Pharmacy Craiova
• Principal subjects/occupational skills covered
  General Ultrasound Course

• Dates (from – to)  1971 - 1976
• Name and type of organisation providing education and training
  University of Medicine and Pharmacy, Craiova
• Principal subjects/occupational skills covered
  Medical School - General Medicine
• Title of qualification awarded
  Graduate Studies, Major: General Medicine
• Dates (from – to)  1965 - 1969
• Name and type of organisation providing education and training
  „Frații Buzești” College - Craiova, Romania
• Title of qualification awarded
  Highschool degree

PERSONAL SKILLS
AND COMPETENCES
Acquired in the course of life and career but not necessarily covered by formal certificates and diplomas.

OTHER LANGUAGES

OTHER LANGUAGES

ROMANIAN

ENGLISH

FRENCH

ITALIAN

TECHNICAL SKILLS
AND COMPETENCES
With computers, specific kinds of equipment, machinery, etc.

Competent with most Microsoft computer programmes – Windows, MS Office Internet skills
ADDITIONAL INFORMATION

PUBLISHED PAPERS AS AUTHOR IN MEDICAL CONFERENCES AND PUBLISHED IN ABSTRACT


Mușetescu C, Bărbulescu Andreea, Ciurea T, Rogoveanu I. Alcoholic cirrhosis-interrelations between the markers of alcohol consumption and aminotransferases, A 3-a conferință a doctoranzilor în medicină și farmacie. Târgu Mureș, 7-9 iulie 2010

C.Mușetescu, Andreea Bărbulescu. Aprecirea eficienței tratamentului cu propranolol la pacienții cu ciroză hepatică și varice esofagiene. Zilele UMF Craiova, 4-5 iunie 2010