

REVIEW

Alcoholic Liver Disease from the Clinical Point of View

Vassilios A. Sevastianos, MD,¹ Spyros P. Dourakis, MD²

¹Department of Internal Medicine and Hepatology, Evagelismos General Hospital, Athens, Greece

²Second Department of Internal Medicine, Hippokrateio Hospital, Athens University School of Medicine, Athens, Greece

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ABBREVIATIONS

ALD: Alcoholic liver disease
 DALYs: disability-adjusted life years cases
 AH: alcoholic hepatitis
 HCC: hepatocellular carcinoma
 ERCP: endoscopic retrograde cholangiopancreatography
 CDT: carbohydrate-deficient transferrin
 EtG: ethyl glucuronide
 CRP: C-reactive protein
 NAFLD: non-alcoholic fatty liver disease
 NASH: steatohepatitis
 MELD: Model for End-stage Liver Disease
 INR: International Normalized Ratio
 FSR: fibrin split products

Correspondence to:

Vassilios Sevastianos, MD,
 3 Louizis Riankour street, 11523,
 Athens, Greece;
 Tel./Fax: +30 210 6919912,
 Mob: +30 6973 795493;
 E-mail: vsevastianos@gmail.com

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ABSTRACT

Liver disease is responsible for more than 55% of deaths resulting from alcohol abuse, while the prevalence of alcoholic liver disease (ALD) is closely correlated with per capita alcohol consumption. ALD represents a wide range of histological changes ranging from simple steatosis to heavier forms of liver injury including alcoholic hepatitis (AH), cirrhosis and/or the concurrent development of hepatocellular carcinoma. These alterations of the hepatic parenchyma do not necessarily reflect distinct stages of the liver disease progression, but rather a continuum relating to histological changes that may be observed simultaneously in the same patient. The fact that only 35% of patients with heavy alcohol abuse develop advanced stages of liver disease, suggests that in the pathogenesis of ALD several other factors are involved that include gender, obesity, drinking patterns, dietary factors, non-sex-linked genetic factors and smoking. Also, long-term drinking can affect the non-alcoholic fatty liver disease and other hepatic disorders, such as hemochromatosis, synergistically with hepatitis B or C and/or with the human immunodeficiency virus. The diagnosis of ALD is based on a combination of findings, including the history of significant alcohol consumption, the clinical evidence of the concomitant liver injury and the support of the clinical case from the resultant histological, imaging and laboratory findings. The beneficial effect of the AH treatment with corticosteroids occurs in patients with encephalopathy or with poor prognosis based on the various grading and prognostic systems of gravity, while the harmful effect is prominent in patients with milder disease, as they manifest an increased risk of infections compared with those not receiving corticosteroids. In patients with alcoholic hepatitis that cannot take corticosteroids for various reasons and in those with the onset of functional renal failure (“hepatorenal syndrome”), use of pentoxifylline is recommended.

1. INTRODUCTION

Humans have been drinking alcoholic beverages at least since the Neolithic period. For more than 10,000 years, beverages which have undergone alcoholic fermentation (alcohol concentration of less than 16%) represent for the Western civilization a source of fluids and energy, particularly during those periods when drinking water from nature was unsafe, while the boiling water practice had not yet prevailed. However, the morbidity of the alcohol use or abuse sharply rose when the production of wine and

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distilled spirits received a wide acceptance in Europe, around the sixteenth century AD.¹

Alcoholic liver disease (ALD) represents the oldest form of liver damage known to humans.² It includes a broad spectrum of liver parenchyma lesions ranging from simple steatosis to severe cirrhosis and hepatocellular carcinoma. Alcohol abuse represents a significant background for morbidity development from organic systems or organs other than the liver that are often co-expressed in the same patient.^{1,3} Today alcohol toxicity ranks as the third most frequent cause of morbidity and mortality, from a potentially preventable and socially acceptable harmful agent. It accounts for 3.8% of deaths worldwide and 4.6% of disability-adjusted life years cases (DALYs).⁴ Recent data from the CDC and the US Prevention indicate that 80,000 Americans died between 2001 and 2005 because of alcohol abuse. Interestingly, these deaths and the non-fatal disease impacts of alcohol consumption drained significant resources from every economy, that was more than \$ 257 million in 2006, in the case of US economy.¹

Thus, since liver disease and other complications related to alcohol consumption are entirely consequences of human behavior, any intervention aimed to inform and the raising awareness of the nature and risks of abuse is imperative, beneficial and can yield significant scientific and social benefits.

2. EPIDEMIOLOGY

The actual prevalence of ALD is tough to assess in the general population. Recently, with the use of liver elastography as a screening tool, alcohol emerged as an underlying cause for a third of the cases with advanced hepatic fibrosis in the general population.⁵

It seems that liver disease is responsible for more than 55% of deaths from alcohol abuse while the prevalence of ALD appears closely correlated with per capita alcohol consumption¹. It is estimated that for every one-liter-increase in per capita use of alcohol, the incidence of cirrhosis grew by 14% in men and by 8% in women.⁶

The highest prevalence of alcoholic liver disease in Europe has been recorded in the United Kingdom in parallel with the eastern and southern European countries. More accurately, in half of the European countries including Austria, France, Germany, Italy, Portugal, and Spain, as well as in two Eastern European countries (Romania and Hungary), a sharp decline in mortality from alcoholic cirrhosis has been observed in the recent years. By contrast, in Western European countries such as Finland, Ireland, the United Kingdom and in most Eastern European countries including Estonia, Poland and Russia, the mortality rate from cirrhosis followed a continuous upward trend, as did the percentage of patients who required hospital care. It is interesting that the largest differences in consumption among these countries are more pronounced at

ages over 45 years while the incidence is two to three times higher in men than women.^{4,7} However, a study that included 13,000 Danish women showed a greater chance of developing cirrhosis compared with males for a given consumption of ethyl alcohol.⁸

However, the published epidemiological evidence of alcoholic disease in Europe probably underestimates the actual burden of the problem. Data from the European Liver Transplant Registry indicate that the number of transplants due to alcoholic disease today follow an increasing trend. At the same time, alcohol abuse is the second leading cause for liver transplantation and in one-third of cirrhosis cases, it has led to transplantation in the European continent.⁹

There are significant differences in the prevalence and the mortality associated with ALD between different ethnological groups. Countries with large Muslim communities have lower alcohol consumption rates and ALD. In the United States, alcohol consumption per capita is 7.5 to 9.9 liters per person per year and the ALD displays intermediate prevalence between of what is observed in the countries with the lowest and those with the highest consumption rates.¹ Indeed, the maximum mortality rate from alcoholic cirrhosis has been recorded among white Hispanic, followed by non-Hispanic black, white non-Hispanics and Hispanics blacks. In women, the correlation is scaled by the largest percentage in non-Hispanic black, and then the white Spanish-speaking, white non-Hispanic and at the end of Spanish-speaking black.¹⁰ Therefore, the literature data show differences in alcohol consumption among different ethnological or social groups.¹¹ However, it remains unclear whether the differences in the percentage of alcoholic cirrhosis and ALD recorded, represent genetic peculiarities, differences in the amount and type of alcohol consumed or characteristics of socioeconomic status and accessibility of medical services in each country.

Despite the strong association between alcohol consumption and the incidence of liver disease, severe alcohol liver disease develops in only a small minority of patients with abuse. In the Dionysus study, the possibility alcohol-related liver toxicity was significant with the consumption of more than 30 gr per day, while those who consumed more than 120 gr experienced cirrhosis more frequently. However, only 2.2% of the high-risk individuals had liver cirrhosis in this study,¹² which underlines the idiosyncratic nature of the liver damage or the presence of differences of other nature in the alcohol receptiveness.

On the other hand, mortality from liver cirrhosis in France between 1925 and 1964 was estimated at 14 per 100,000 individuals who consumed less than 80 gr of alcohol per day and 357 per 100,000 among those who drank more than 160 gr per day. It seems, therefore, that those who consume between 80 and 160 gr of alcohol a day bear a significant risk of developing progressive liver disease including alcoholic hepatitis and cirrhosis.^{1,13} But in a more recent meta-analysis, an increased

likelihood of loss of life from liver cirrhosis was found among men - women who consumed between 12 and 24 gr alcohol daily.¹⁴

Therefore, it is shown that there is probably a lower limit on alcohol consumption, beyond which the risk of development and progression of liver disease is significant.¹⁴ This threshold is probably very low and probably difficult to document because of the difficulties to record in the general population consumptions from 10-12 gr of alcohol per day.⁴ However, the effects of binge drinking on the organism in general are still unknown (drinking five or more drinks for men and four or more for women).¹⁵

3. NATURAL HISTORY OF ALCOHOLIC LIVER DISEASE AND RISK FACTORS

ALD represents a broad variety of disorders, ranging from simple steatosis to more severe liver injury including alcoholic hepatitis (AH), cirrhosis, or the parallel development of hepatocellular carcinoma (HCC).¹⁶ These lesions of the hepatic parenchyma do not necessarily reflect distinct stages of liver disease progression, but rather involve a continuous spectrum of parenchymal changes that can be observed simultaneously in the same patient (Figure 1).¹⁷ Indeed, the advanced stages of progression of the liver disease associated with the presence of more specific histological findings include Mallory bodies, megamitochondria or perivenular and perisinusoidal fibrosis.¹⁸

Fatty liver characterizes an early organ response to alcohol hit observed in more than 90% of the heavy abuse, with the presence of mild hepatocyte steatosis in the zone 3 (perivenular). It can also affect the respective 2 or even the zone 1 (periportal) in the cases with more significant liver damage. Interestingly, only one-third of people with severe abuse develop more severe forms of ALD such as advanced fibrosis and cirrhosis. In patients with underlying ALD and heavy alcohol consumption one can observe, at the clinical level, recurrent episodes of alcoholic hepatitis (AH) that can lead to the development of portal hypertension and liver

failure with high rates of short-term mortality.¹⁶

The fact that only 35% of patients with severe alcohol abuse develop advanced stages of liver disease, rather suggests that in the pathogenesis of ALD some other factors are also involved (Table 1, 2).¹⁶ Several risk factors have been identified, and these include gender, obesity, the drinking patterns, dietary factors, non-sex-linked genetic factors, and smoking. Female gender is one of the well-documented bear for the ALD development, which can be attributed to the lower levels of alcoholic dehydrogenase in the gastric fluids, the higher percentage of body fat and the presence of estrogen which characterizes female gender. Obesity is another important factor that accelerates the development of both fibrosis and cirrhosis. Experimental studies show that the synergistic effects of obesity and alcohol abuse include among others the response of endoplasmic reticulum system to stress, the type I macrophage activation and the resistance to adiponectin.^{3,16,19,20}

TABLE 1. Risk factors for the development of alcoholic related cirrhosis.²²

• Men >60-80gr/d
• Woman >20gr/d
Every day use
Alcohol outside meals
Binge drinking
No wine
Female gender
Race
Concurrent viral hepatitis (hepatitis C)
HIV infection
Increased body weight and insulin resistance
Smoking
Hemochromatosis
Genetic factors

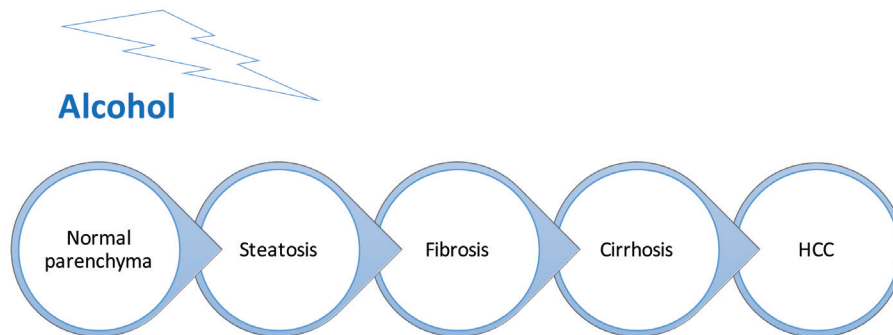


FIGURE 1. Natural history of alcoholic liver disease.^{12,22,25,28,37}

TABLE 2. Genes involved in the development of alcoholic related cirrhosis.²²

Genes involved in alcohol metabolism <i>ADH1B</i> <i>ADH1C</i> <i>CYP2E1</i> <i>CYP1A1</i> <i>ALDH2</i>	Conflicting results for all variants; data from meta-analysis suggested no association with ALD
Genes related to oxidative stress <i>GSTM1</i> <i>GSTP1</i> <i>GSTT1</i> <i>MnSOD</i> <i>NAT</i> <i>HFE</i>	Mostly negative studies; positive associations challenged by failure to replicate in subsequent studies; MnSOD variation may be associated with hepatocellular carcinoma (to be confirmed indecently)
Genes implicated in immune reactions <i>TNFA</i> <i>Interleukin (IL)-10</i> <i>IL-1R</i> <i>IL-1b</i> <i>CD14 receptor</i> <i>CTLA-4</i> <i>TLR-4</i>	All conflicting or yet unconfirmed except for TNFA-238A allele which was found to be associated with ALD in several independent studies and by meta-analysis; and CD14 variation which was linked to ALD in three studies
Genes coding for fibrosis associated factors <i>TGFb1</i> <i>MMP3</i>	No association in sufficiently powered genetic case-control studies
Genes involved in the modulation of steatosis <i>PPARg</i> <i>MTP</i> <i>ApoE</i>	Yet unconfirmed single studies of PPARg and MTP variants with low sample sizes showing significant association with ALD; ApoE with conflicting data from two very small studies
Miscellaneous <i>NFkB1</i> <i>DRD2</i> <i>SLC6A4</i>	Single study showing association of NFkB1 variant 94 ins/del with fibrosis; DRD2 and SLC6A4 negative

Daily or almost daily heavy drinking which starts at an early age increases the risk of serious ALD development compared with episodic or binge drinking. Some genetic factors appear to influence the development of ALD, but currently little data are available in the literature. Changes in the genes encoding antioxidant enzymes, cytokines, other inflammatory mediators and enzymes that metabolize alcohol may play a role in pathogenesis.²⁰ Indeed, recent studies show that changes in polymorphism of TNF-238A²¹ and PNPLA3 protein (patatin-like phospholipase domain-containing protein 3)²² may influence the development of alcoholic cirrhosis in white patients who abuse alcohol, but these data require more literature documentation.

Also, long-term drinking can interfere synergistically with viral hepatitis B or C and human immunodeficiency virus, the non-alcoholic fatty liver disease and disorders such as hemochromatosis that accelerate the progression of liver disease at more advanced stages probably through activation of multiple mechanisms.^{16,23} Specifically, it appears that patients with hepatitis C who consume more than 30-50 gr of alcohol per day have a four-fold increased risk of developing liver fibrosis while those who drink excessive alcohol have 30 times greater risk of developing cirrhosis.⁴

On the other hand, the presence of iron in the liver biopsy specimens has also been associated with the development of fibrosis in ALD, and with increased mortality in alcoholic cir-

rhosis. Elevated levels of iron in serum is not uncommon in patients with ALD compared with alcoholics without underlying liver disease. However, while there are studies which have described a liver disease correlation with the mutation H63D, there is not a respective definite correlation with mutations in C282Y HFE gene. Of course, alcohol and iron may act synergistically to produce oxidative stress and thus to accelerate the progressive liver damage.²⁴

4. DIAGNOSIS OF ALD

The diagnosis of ALD is based on a combination of findings, including the history of significant alcohol consumption and the evidence of the related liver injury. Furthermore, the clinical suspicion may support the corresponding histological, imaging and laboratory findings. Alcohol abuse is usually denied by patients while semiological features of abuse are present. Physicians often underestimate the problem with the result, not rarely seen, alcohol abuse to be revealed as reality by the consequences and complications.²⁵

Both clinical and laboratory findings of ALD may be non-diagnostic, especially in patients with mild ALD or early stages of alcoholic cirrhosis. Therefore, the clinician should be sensitized in detecting ALD resorting to the search for specific information from other family members or even through questionnaires combined with the laboratory evidence that can support the clinical suspicion.

4.1. CLINICAL PICTURE

The findings on physical examination in ALD patients vary considerably and have low sensitivity, even in detecting advanced disease or cirrhosis. Although particular clinical findings are observed more frequently among people with ALD, such as swelling of the parotid, the contraction of the palmar fascia and signs of male feminizing, however, even those are not specific³. On the other hand, the detection of hepatic encephalopathy, dilated veins in the anterior abdominal wall, ascites, presence of spider nevi and the feeling of weakness have been associated with an increased risk of life loss during the next year.²⁶

Alcoholic hepatitis is manifested clinically by anorexia, fever, and jaundice. On physical examination one may find tender hepatomegaly (due to deposition of fat and protein in hepatocytes),²⁷ relatively small spleen enlargement (the opposite happens in cirrhosis on the grounds of hepatitis), ascites and loss of proximal muscle mass. Hepatic encephalopathy and renal failure of functional type ("hepatorenal syndrome") can coexist.²⁸ In the right hypochondrium, there is often (50%) an audible murmur (suggesting enhanced hepatic arterial perfusion). Indeed, in a reference study including 101 patients with alcoholic hepatitis, the murmur was verified in 58% of the patients.²⁹ The fever (38-38,5 °C) could be attributed to the

alcoholic disease after ruling out the presence of infection that often coexists.²⁸ The clinical picture of alcoholic hepatitis mimics an acute cholecystitis with fever, jaundice, and leukocytosis added on a preexisted hepatomegaly.²⁵

The simultaneous presence of fever and lymphocytosis can mislead the clinician towards the septic syndrome, especially if the patient's history is unclear. On the other hand, malnutrition and comorbidities often coexist in the same patient with an advanced liver disease, predisposing to the development of infections, and imposing, at least, the necessity of taking blood and urine cultures, obtaining a chest radiograph, and evaluating the ascitic fluid, if present.³⁰

Also, one can often observe unexplained intrahepatic and extrahepatic cholestasis due to the obstruction of the lower third of the bile duct from fibrosis due to the accompanying chronic pancreatitis.²⁵ This finding should be evaluated carefully on the basis that if endoscopic retrograde cholangiopancreatography (ERCP) is performed in these cases, it incurs a significant risk for the development of severe necrotizing pancreatitis and, therefore, it should not be carried out for purely diagnostic reasons.³⁰

It is worth noting that the clinician must take into account that ALD often coexists with manifestations from other organs or systems including malnutrition and muscle mass loss, alcoholic cardiomyopathy, pancreatic dysfunction and neurotoxicity from alcohol abuse.³

4.2. LABORATORY FINDINGS

Currently, there is no specific biological marker to associate alcohol with the underlying cause of liver damage. Several laboratory parameters used in clinical practice have been linked with chronic alcohol use and alcoholic liver damage. Indeed, the sensitivity of carbohydrate-deficient transferrin (CDT) and γ GT to evaluate the drinking of greater than 50gr per day is 69% and 73%, respectively. These rates are significantly higher than that of AST (50%), ALT (35%) and MCV (52%),³¹ while the combination of CDT and γ GT shows much greater sensitivity, reaching near 90% (Figure 2).³²

γ GT is usually higher in ALD patients compared to those who suffer from other liver diseases. Given the lower cost of the assay, it remains the laboratory test most commonly used in clinical practice. However, 1/3 of individuals with heavy alcohol use have γ GT values within the normal limits in serum, even in cases of excessive consumption.³³ Additionally, the γ GT serum activity loses its sensitivity in more advanced liver disease because the activity is often found increased in patients with extensive fibrosis, regardless of the underlying etiology. Recently it was found that the γ GT levels in serum are affected not only by the amount of alcohol consumed but also by body mass index and gender.³⁴ Lower γ GT levels <100 IU/L or the ratio of total bilirubin/ γ GT >1 have been proposed as predictors of increased mortality rates within one year in patients with alcoholic cirrhosis.³⁵ Also, direct metabolites of alcohol

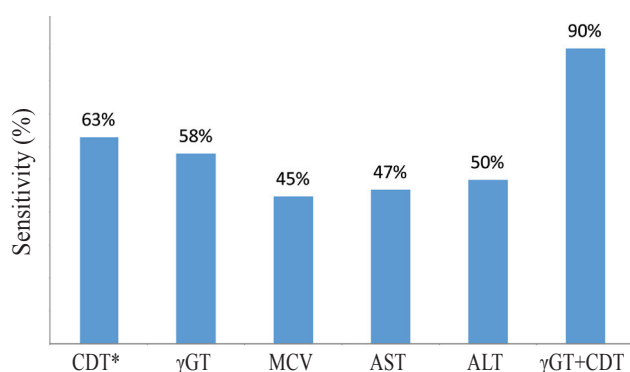


FIGURE 2. Sensitivity of biochemical markers to detect severe alcohol abuse.³²

have been studied and used as biological markers of abuse, such as the determination of ethyl glucuronide (EtG) showing sensitivity and specificity of 92% and 91% respectively.³⁶

Alcoholic hepatitis is characterized by increased aminotransferase (transaminase) greater than twice the upper limit of normal ($>2XULN$), but it always remains <300 U/L, with the ratio of AST (aspartate aminotransferase or glutamic oxaloacetic transaminase SGOT) to ALT (alanine aminotransferase or glutamic pyruvate transaminase SGPT) is typically >2 in more than 70% of cases.^{25,28,36,37} The above typical picture is attributed to a lack of pyridoxine (vitamin 6) that is a cofactor for the ALT enzyme activity and to the increased mitochondrial AST.

ALT levels >500 U/L exclude the diagnosis of alcoholic hepatitis. Higher values should raise the suspicion of, concurrent with alcohol abuse, viral, ischemic or drug-related (e.g., by taking a relatively large amount of paracetamol) hepatitis. Attention is needed in the interpretation of the increases in serum transaminases levels owing to an extrahepatic origin (rhabdomyolysis, myocardial infarction, etc.).

While the above mentioned may coexist, increasing IgA, leukocytosis with neutrophilia (maybe at levels of leukemoid reaction: $>50.000/mm^3$), increased C-reactive protein (CRP), and hyperbilirubinemia (>5 mg/dl) with predominance of the direct type, can also be present. The latter typically increases more with the coexistence of renal failure or hemolytic anemia. Note that γ GT is often found significantly increased (70%) due to its activation. Also, macrocytosis (MCV >100 fl) may be observed owing to the absence of B12 and folate deficiencies, alcohol toxicity on maturing erythrocytes and impaired lipids on the membranes of erythrocytes (red cells “as spurs” - spur-cell). Often thrombocytopenia is present because of bone marrow suppression from ethanol toxicity or sequestration of platelets in the splenic reservoir due to portal hypertension and splenomegaly (hypersplenism). There may be a prolongation of prothrombin time because of liver failure that cannot correct despite the parenteral adminis-

tration of vitamin K. Also, often hyperuricemia coexists (in severe hepatic impairment shows hypouricemia) as well as hypokalemia of multifactorial etiology (vomiting, but mostly from the toxic effect of ethanol on urinary tubules). Serum ferritin can increase, consequential to its release from the hepatocytes because of inflammation but also related to the extent of liver fibrosis.^{25,28,37} The ferritin levels in the serum are normalized after a few months of abstinence from alcohol and the improvement of inflammatory activity in the liver.³⁸ Erythrocyte sedimentation rate and serum CRP levels can increase because of the presence of polyclonal hypergammaglobulinemia typically seen in chronic liver disease. The serological markers of hepatotropic viral infections and the absence of autoantibodies could exclude concurrent viral or autoimmune liver diseases. Autoantibodies (antinuclear and against smooth muscle fibers) are often found in low titers ($<1/160$), but not accompanied by a significant increase of gamma globulins. If higher serum titers of these autoantibodies or hypergammaglobulinemia are found, histological examination is essential for establishing the diagnosis and the marginalization of coexisting autoimmune liver disease.

An increase in creatinine >1.5 mg/dl and the reduction of the creatinine clearance <40 ml/min are indications of hepatorenal syndrome representing an adverse prognostic marker for the disease progression. However, in cirrhotic patients, creatinine and urea in serum underestimate the severity of the renal impairment. The latter may be attributed to the presence of hyperbilirubinemia (technical problems in the biochemical measurement), to the blood volume increase due to the concomitant dilution, to the hypo-protein feeding, and the reduced urea synthesis from a dysfunctional liver parenchyma. Furthermore, a significant role may be assigned to the malnutrition typically observed in these individuals with the parallel decrease in muscle mass and consequent endogenous creatinine decline production. Because of the above, a much greater reduction is required in glomerular filtration rate for the corresponding increase in urea and creatinine to become apparent. In contrast, the increase in blood urea could be attributable to gastrointestinal bleeding, to intense catabolism or corticosteroids intake.^{25,28,37}

4.3. IMAGING STUDIES

Imaging studies provide valuable information. Ultrasound, CT, and MRI can be used as tools for the presymptomatic detection of fatty liver, but do not contribute to the determination of the exact etiology of the underlying liver disease. However, they can support decisively the exclusion of other causes of the impaired liver biochemistry such as the obstructive biliary lesions or the presence of invasive liver neoplasms.^{3,4}

The liver ultrasound usually shows diffuse echogenic liver parenchyma. The infiltration of the liver parenchyma with fat reduces hepatic attenuation compared with spleen on non-contrast imaging. Indeed, in the CT study of the liver

without intravenous contrast, the liver appears enlarged and hypodense in contrast to the corresponding picture of the spleen and kidney, while intrahepatic branches of portal and hepatic veins are most conspicuous than that of the healthy liver. The findings are like those observed in non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH). Focal fat concentration in the liver parenchyma presents on CT imaging as hypodense area ("pseudo-tumor") and may be confused with certain liver tumors while for the differential diagnosis an MRI must be performed. The findings as mentioned earlier could coexist with that of liver cirrhosis (irregularity of the external contour of the liver, enlarged caudate lobe, thickening of the gallbladder wall, ascites, splenomegaly, portosystemic shunts). An additional Doppler ultrasound study shows an increase in the speed of hepatic artery blood flow or an increase in its diameter.^{25,28,37}

Among these methods, ultrasound probably has the lowest sensitivity and specificity, particularly when steatosis on histologic level does not exceed the limit of 20-30% of the hepatic parenchyma. MRI and MR spectroscopy are reliable tools for assessing the degree of steatosis, but the lack of standardization of these methods and their high costs limit their use and availability.⁴

4.4. THE POSITION OF THE TRANSIENT ELASTOGRAPHY IN ALD

Measuring liver stiffness appears to be a valuable tool for the assessment of hepatic fibrosis also in patients with ALD. However, in studies that did not consider the coexistence of alcoholic steatohepatitis, the lower value of the stiffness index corresponding to F3 and F4 fibrosis stage in histological level was significantly higher compared to that verified in patients with viral related liver diseases. Also, several studies have shown that patients with alcoholic cirrhosis had significantly higher stiffness values compared to those who suffered from cirrhosis secondary to viral infection, underscoring the fact that the causative agent can greatly affect the extent and the progression of fibrosis in the liver.⁴

Therefore, the liver stiffness index can be correlated with the stage of fibrosis in ALD, but the diagnosis of advanced-stage liver disease, severe fibrosis or cirrhosis, probably requires a higher lower limit of the index as compared with other liver diseases. Increased liver stiffness index can also be observed in cases of alcoholic disease and concomitant increase of aminotransferase levels above 100 IU/L, but in these cases, it should be interpreted with great caution.³⁹ Possibly the different distribution of fibrosis in the liver and the cholestasis, the liver enlargement, the inflammation, and hepatocytes necrosis as the result of acute hepatocellular injury could give a satisfactory explanation of this phenomenon.⁴⁰ Thus, heavy alcohol abusers with or without the presence of alcoholic hepatitis can experience an increase liver stiffness index leading to an inaccurate estimate of fibrosis, a datum that should be noticed

by the clinical hepatologist, as the liver stiffness index in ALD has not yet been standardized.

4.5. LIVER HISTOLOGY IN ALD

Although liver biopsy does not significantly contribute to the management of patients with ALD, in some cases it is useful, considering that more than 20% of patients with a history of alcohol abuse have a secondary or other coexisting cause of liver damage. Also, on a well-compensated liver disease, the biopsy can capture the stage and the severity of liver disease.³

Alcoholic liver disease is associated with three main histological lesions in the liver that often coexist (steatosis, steatohepatitis, cirrhosis). A total of 80% of patients with alcohol abuse present histologically liposis, 10-35% steatohepatitis and 10% cirrhosis. On hematoxylin-eosin staining, many hepatocytes are foamed with fat droplets in the protoplasm and vacuolar nucleus displaced to the cell membrane. The lesions are most pronounced around portal spaces (zone 1 of the hepatic lobules). The droplets of fat are stained with oil red O in cryostat sections. During the fixation of the liver biopsy specimens, in a formalin solution, the fat droplets dissolve and thus are shown as empty areas within hepatocytes. Also, liposis in the liver parenchyma, is expressed as ballooning degeneration of the hepatocytes, containing the nucleus near amorphous eosinophilic Mallory bodies, with the presence of giant mitochondria, but one can also see an infiltration of parenchyma by polymorphonuclear neutrophils. The degree of polymorphonuclear cell infiltration has a poor predictive value and can coexist with mononuclear cells. There is typical presence of pericentral (around the central vein, in zone 3 of the hepatic lobules) and perisinusoidal fibrosis (in the space of Disse). Fibrosis can extend in the portal areas or other central vessels forming central-central and central portal bridges. Fibrosis represents the result of connective tissue production by cells of Ito (stellate cells) and may be followed by the accumulation of material, like the composition of the basement membrane of capillaries, culminating in the capitalization of sinusoidal in the case of micro-nodular liver cirrhosis. The histological features of NASH may be identical to those observed in alcoholic hepatitis.^{25,28,37}

4.6. DIFFERENTIAL DIAGNOSIS

Diagnosis is based on clinical presentation (jaundice, ascites, tender hepatomegaly, increased transaminase <300U/L, the ratio AST/ALT >2, leukocytosis with polymorphonucleates) in an individual with alcohol abuse. In some cases, you may need an interaction with family members or the working environment to confirm the abuse. Histology studies may be useful for prognostic purpose, but are not necessary for the diagnosis.

Differential diagnosis includes NAFLD/NASH, acute or chronic viral hepatitis, acute drug-induced hepatitis, fulminant Wilson disease, autoimmune hepatitis, acute cholecystitis,

hepatic abscess, and hepatocellular carcinoma. Caution is also needed in the differential diagnosis of the liver manifestations of the alcoholic cardiomyopathy that can exist or co-exist with alcoholic hepatitis/cirrhosis. The differential diagnosis of the ethanol withdrawal syndrome by hepatic encephalopathy complicating alcoholic hepatitis is of great importance for treatment management while based primarily on semiology of the sympathetic system stimulation. Alcoholic hepatitis is a febrile illness with concomitant leukocytosis with polymorphonucleates elevation, in parallel with an increase in CRP levels and needs a careful differential diagnosis of possibly concurrent bacterial infections that may worsen with the therapeutic management (corticosteroids).^{25,28,37} It has been suggested that procalcitonin in the serum that rises in infections but not in alcoholic hepatitis could help in the differential diagnosis.⁴¹

5. ALD PROGNOSIS

The prognosis depends primarily on the patient's decision to stop alcohol use. However, avoiding alcohol use is often manifested by a temporary worsening of the clinical condition despite the abstinence. Patients with alcoholic hepatitis exhibit a mortality rate of 40% even with the best treatment. Poor prognostic factors include leukocytosis, severe fibrosis, ascites, encephalopathy, functional renal failure ("hepatorenal syndrome") and coagulopathy. In most patients with less severe forms of alcoholic hepatitis who abstain from alcohol use, we can see a clinical and laboratory improvement in a few months.

There have been proposed various systems for the assessment of alcoholic hepatitis clinical severity [Maddrey index, Glasgow score, MELD (Model for End-stage Liver Disease), Lille model score] to select the appropriate patients who may benefit from treatment with corticosteroids (Table 4 and 5). These systems include common parameters (bilirubin, prothrombin time). The known prognostic classification score Child-Turcotte-Pugh used for staging the severity of cirrhosis is not accurate for alcoholic hepatitis.

The Maddrey discriminant function (4,6 X prolongation of prothrombin time in seconds + bilirubin in mg/dl) is the oldest and most widely used. Although it includes the measurement of prothrombin time in seconds compared to the control but not the INR (International Normalized Ratio) that is the modern way of evaluation internationally (was devised to standardize the results among laboratories). The survival in those with Maddrey index <32, is about 90%, so the side effects of using steroids exceed the expected benefit from the treatment intervention.

The Glasgow alcoholic hepatitis score (not to be confused with the Glasgow coma scale) is based on five parameters: age, white blood cells, urea, bilirubin and prothrombin time (Table 3). The score helps in predicting and distinguishing those with Maddrey index patients >32 who will benefit most from the

use of corticosteroids. Glasgow score value >9 correlated with poor prognosis in 1 and three months. Those who had Maddrey index >32 and Glasgow score >9 but received corticosteroids had three-month survival 60% versus 40% of those on only conservative treatment.

The MELD score [3.8 [10log serum bilirubin (mg/dL)] + 11.2 [10log INR] + 9.6 [10log serum creatinine (mg/dL)] + 6.4, www.mayoclinic.org/meld/mayomodel7.htm, www.unos.org/resources/MeldPeldCalculator.asp?index=98] is a statistical model used to predict survival in patients with cirrhosis while on the waiting list for a liver transplantation in the US. Several studies showed that the MELD score is as good or better than Maddrey score for assessing the severity of alcoholic hepatitis. Scores >11 are associated with increased mortality

TABLE 3. Glasgow scoring system.^{25,28,37}

	Grade		
	1	2	3
Age	<50	≥50	-
WCC (10 ⁹ /L)	<15	≥15	-
Urea (mmol/L)	<5	>5	-
INR	<1,5	1,5-2	>2,0
Bilirubin (μmol/L)	<125	125-250	>250

TABLE 4. Prognostic systems of short-term survival in alcoholic hepatitis.^{25,28,37}

	Grades	28-day survival
Maddrey score	< 32	93%
	>32	68%
Glasgow alcoholic hepatitis score	<9	87%
	>9	46%
Model for end stage liver disease (MELD) score	<11	96%
	>11	45%

TABLE 5. Prognostic systems for three-month survival in alcoholic hepatitis.^{25,28,37}

Markers	Mortality
Hepatic encephalopathy	>50% at 3 months
Maddrey score	>35% at 2 months when >32
MELD score	>50% at 3 months when >25

from alcoholic hepatitis and value >21 with a 3-month mortality rate of 20%, and puts the indication for corticosteroid therapy. Additionally, the score could be assessed during the patient's hospital admission and after one week to determine the prognosis.

The Lille score (www.lillemodel.com), considers six variables: bilirubin, creatinine, prothrombin time in INR, age, albumin and bilirubin change as a response to one-week corticosteroid treatment. If there is no response to treatment, corticosteroids can be stopped since they are outweighed by their potential side effects (particularly infections).^{25,28,37}

In a study from the 2nd University Department of Medicine, University of Athens, including 34 patients with alcoholic hepatitis, the total mortality at 30 and 90 days was 6% and 15% respectively. The accuracy of predicting survival was confirmed by models Maddrey and MELD. Also, the AST levels, fibrin split products (FSR) and CRP values in serum showed a significant correlation with the survival.⁴²

Alcoholic hepatitis represents a poor prognostic factor in patients with cirrhosis, because when it coexists in the same patient, the total annual mortality rate is 26% compared to 7% in cirrhosis without steatohepatitis.^{25,28,37}

6. TREATMENT

Immediate cessation of alcohol use is recommended with the support of the family, the social service and the specialized psychiatrist. Complete cessation of alcohol leads to regression of fatty infiltration (in 4-6 weeks), inflammation and possibly connective tissue that had developed, which is crucial for reducing the portal system pressure.

The role of corticosteroids in the treatment of alcoholic hepatitis was controversial for a long time. The beneficial effect manifested in the groups of patients with severe disease, namely in patients with encephalopathy or poor prognosis per different scoring systems of severity. On the other hand, the deleterious effect is significant in patients with milder disease, as they exhibit an increased risk of infection compared to patients who do not receive corticosteroids. A recent systematic review yielded an overall negative result but was positive for the use of corticosteroids for those with Maddrey score >32 or hepatic encephalopathy. It is now accepted in patients with alcoholic hepatitis, and hepatic encephalopathy, when Maddrey index is >32 or the MELD score >21 , to administer corticosteroids (prednisolone 40 mg/day for four weeks) if the patient does not exhibit gastrointestinal bleeding or infection. Corticosteroids should not apply to patients with Maddrey index <32 or MELD <21 . Patients who experience a decrease in bilirubin levels after 6-9 days of treatment show significant and sustained response in parallel with a good prognosis. The mortality rate in the group of patients who have not demonstrated a drop-in bilirubin levels in the same period was 36.8%

and 57.9% at 28 and 56 days while those who achieved a bilirubin decline by 25%, the corresponding mortality rate was 0 and 11.1%. Up to 40% of patients with alcoholic hepatitis do not respond to treatment with corticosteroids. One must treat five patients to save only one. Lille score >0.45 indicates non-response to corticosteroids resulting in six-month survival $<25%$. Prednisolone is preferred because it does not need to be metabolized in the liver, as prednisone does. In patients with pancreatitis, gastrointestinal bleeding or renal impairment, corticosteroid use has not been studied. The risk of infections development during steroid treatment is critical, and close clinical monitoring is required.

The increased disposal price of anti-TNF- α compounds in patients with alcoholic hepatitis led medical community to the use of pentoxifylline. Pentoxifylline is an anti-TNF agent but may act through another mechanism because it does not change the levels of the cytokines. It is administered as Tarantal[®], in tablets, per os, at a dose of 400mg, three times daily for 28 days. It is recommended for patients that cannot take steroids and in patients with functional renal failure event ("hepatorenal syndrome"). In patients who did not respond to corticosteroids, pentoxifylline administration was not helpful. The concomitant use of corticosteroids and pentoxifylline does not increase the effectiveness of the intervention.

Initially, alcohol use was considered a contraindication for liver transplantation. But in patients who develop end-stage liver failure, it can be attempted after a complete abstinence from ethanol use for at least six months. During this time, some patients will have died, while others will delist. Thus, those who have not improved within three months of stopping alcohol use, are not expected to improve later, and can be considered potential transplantation candidates. Recurrence of abuse after transplantation is frequent (10.8%). It is necessary to treat alcoholic disease complications such as ethanol withdrawal syndrome, gastrointestinal bleeding, infections, ascites or hepatic encephalopathy.

In patients with ascites one can grant unsalted diet and diuretics, in those with hepatic encephalopathy lactulose and antibiotics against endogenous gut flora (rifaximin) but cases with hepatorenal syndrome will need albumin and terlipressin. Also, one can administer H₂ receptors antagonists or proton pump inhibitors for preventing upper gastrointestinal bleeding.

Usually, patients with ALD are cachectic in a hypercatabolic condition which worsens the prognosis. Good nutrition is essential. In anorectic patients, enteral feeding can be administered with 2000 Kcal/day, with an albumin content of 1.5 gr/kg even in those with hepatic encephalopathy events. Survival can be similar to that observed with corticosteroid treatment. One can also administer B complex vitamins (before the administration of carbohydrates to prevent Korsakoff syndrome) and folic acid (to address possible shortcomings).

Patients with alcoholic hepatitis exhibit susceptibility to

infections, since their polymorphonuclear cells are numerous but functionally inferior. Patients should frequently be examined for the presence of bacterial infection (pneumonia, spontaneous bacterial peritonitis, urinary tract infection) with the appropriate investigations (blood cultures, urine, ascites fluid, chest X-ray).

In patients with severe liver disease and withdrawal syndrome, chlormethiazole (Hemineurin® or Distaneurin®), midazolam (Dormicum®) or lorazepam (Tavor®) can be administered due to a shorter half-time. When psychotic manifestations prevail, neuroleptic drugs should be administered (haloperidol or “atypical” as olanzapine, etc.). The long-term administration of baclofen can help without clinically significant adverse effects.^{25,28,37,43}

7. THE ROLE OF LIVER TRANSPLANTATION IN THE TREATMENT OF ALD

After a long period of reluctance to add patients with ALD to the liver transplant list, a worldwide view is currently formed that transplantation offers an excellent survival advantage in appropriately selected patients, like that observed for other liver transplant indications. The different vision mainly exists since the ALD is a self-inflicted disease, in parallel with the increased likelihood of significant damage with alcohol use to organs other than the liver. Furthermore, in the medical community there dominates the lack of compliance of these patients to the instructions in the postoperative period, and the recurrence of abuse that can lead to early graft failure.^{44,45}

The first primary liver transplant experience in patients with alcoholic cirrhosis started in Pittsburgh wherein survival among 42 transplanted patients was like in other forms of liver disease.⁴⁶ Similar data have also currently been published by other centers. Indeed, the relative survival of patient and graft in another study that included 123 patients was 84% and 81% for the first year, 72% and 66% for the fifth and 63% and 59% for the seventh year after transplantation respectively.⁴⁷ Without liver transplantation five-year survival appears less than 23%.⁴⁸

Clinicians who treat patients with end-stage liver disease due to alcohol abuse, contribute decisively to the success of transplantation when they promptly examine this possibility as a potential option and refer these patients for evaluation at the appropriate transplant centers. A period of six months of abstinence from alcohol is widely used to prevent recurrence while allowing recovery of the hepatic parenchyma by the toxicity of abuse. However, this time-limit cannot be used to distinguish the group of patients who will continue to abstain.³ In a study including 40 patients with ALD admitted to assess the likelihood of liver transplantation, it was found that 38% had a positive urine test for alcohol and 30% for illicit drugs.⁴⁹

However, according to a French study, 26 patients with

alcoholic hepatitis with a high risk of life loss underwent liver transplantation after failure to respond to the conservative treatment. Patients were selected by the existence of a real social supportive environment, no previous episodes of alcoholic liver disease and non-history of severe psychiatric illness. These patients were compared with 26 patients who were randomized as the control group. The cumulative percentage of six-month survival was significantly higher in the transplanted patients (77 compared to 23%). The two-year survival was also significantly higher (71 compared with 23%). Three of the patients who underwent transplantation exposed themselves again to the use of alcohol, one 720 days, one 740 days and one 1140 days after liver transplantation.⁵⁰

In conclusion, liver transplantation represents an alternative for treating selected patients with alcoholic liver disease, even though both transplantation from cadaveric and much more from a living liver donor raise important social and ethical questions.

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