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Review

Alcoholic liver disease – An overview

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Alcoholism is generally recognized to be a major social problem in many parts of the world, especially in the United States and in many European countries. Indeed, statistical data of the last two decades have shown that the number of alcoholics in the United States exceeds 15 million. In addition, Alcoholic Hepatitis and Cirrhosis result in 20,000 – 40,000 deaths annually and constitute the fourth leading cause of deaths among middle-aged Americans.[1] According to recent epidemiological studies, 5 to 10 percent of the general population in most European countries consume large quantities of alcohol. In West Germany more than 1.8 million people are alcoholics.[2]

Alcoholism, however, is not synonymous with Alcoholic Liver Disease (ALD) and recent observations have shown that only 15 to 25 percent of alcoholics finally develop severe liver disease, namely Alcoholic Hepatitis and Cirrhosis.[3] Indeed, there is increasing evidence that in addition to the amount and duration of alcohol consumption, other, acquired and genetic risk factors may predispose to the development of severe ALD.

It has been estimated that 1 unit (10 gr) of alcohol is contained in 28 mL of whisky or other similar strong spirit, in 85 mL of wine, or 230 mL of beer. It is believed that a consumption of 21 units for men and 14 units for women on a weekly basis, is safe. In contrast, 16 units (160 gr) of alcohol daily, for 5 years, seems to be the minimum associated with significant liver injury.[4]

Recent studies have shown that women are more susceptible than men to developing alcohol-related liver injury. ALD develops after a shorter period of drinking and is more severe in women that in men.[5] These **sex differences** are probably due to higher blood concentrations for a given amount of alcohol in women. On average, blood alcohol levels have been found to be 40 percent higher in women than in men who drink equal amounts. It is believed that women absorb alcohol more rapidly and more thoroughly, because they have a lower level of gastric alcohol dehydrogenase (lower first pass effect). Sex-related differences in endocrine function seems to further contribute to a slow metabolism of ethanol, allowing it to remain in the body fluids for a longer period.[6,7]

Besides these sex differences, genetic polymorphism in isoenzymes of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) seem to account not only for different rates of alcohol oxidation, but also for different habitual behavior on alcohol intake.[8]

The role of malnutrition: There is no doubt that malnutrition contributes to the development and probably to the severity of ethanol-induced liver injury. The interactions, however, between chronic alcohol abuse, nutritional status and severity of liver damage, have not been fully understood. Obviously, malnutrition in chronic alcoholics occurs primarily because of the replacement of normal nutrients by the "empty" calories of alcohol, leading to deficiency of folate, thiamine and other vitamins and minerals. In addition, impaired hepatic metabolism of nutrients in alcoholics with liver damage and malabsorption due to gastrointestinal complications, such as pancreatic insufficiency, further contribute to nutritional deficiency in alcoholics. Malnutrition, on the other hand, seems to potentiate ethanol hepatotoxicity at least in certain species of primates and in humans. Indeed, dietary supplements exhibit beneficial effects in the management of patients with severe alcoholic hepatitis. Ethanol and malnutrition probably act synergistically.[9]

The role of hepatitis B and C viral infections: It has been recognized from several studies, that alcoholics with liver disease show an increased frequency of succeptibility to Hepatitis B Virus (HBV), as estimated by the pres-

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ence of antibodies to surface and core antigens in their serum. Mendenhall et al[10] demonstrated, in a study of a significant number of patients with various types of alcohol related liver damage, that almost 30 percent of them were anti-HBs and/or anti-HBc positive. In addition, 3 percent of these patients were found to be actively infected with HBV.

Furthermore, a high frequency of integrated HBV DNA in the genomic DNA of hepatocytes has been documented in alcoholics with cirrhosis and hepatocellular carcinoma (HCC), by using highly sensitive molecular biologic techniques.[11,12]

Using similar molecular approaches, a high prevalence (8 to 45 percent) of anti-HCV antibodies among alcoholics with liver disease, has also been demonstrated. Most of these patients have HCV-RNA detectable in their serum in a rate of 65 to 94 percent, indicating an active viral infection.[13]

Although the high incidence of HBV and HCV infections in alcoholics may reflect a low socioeconomic status or an increased susceptibility of this category of the population to the acquisition of these infections, yet the mechanisms that allow chronic viral infections to persist in alcoholics and the role that HBV and HCV infections may play to the pathogenesis of ALD are still unknown. Recent observations support the concept that chronic ethanol consumption probably suppresses the cellular and humoral immune responses to HBV and HCV viral proteins.[14] In this setting alcohol may enhance the replication of HCV resulting in more severe liver injury. In fact, there is clinical evidence that hepatic inflammation is more prominent in HCV positive patients, who consume large amounts of alcohol and that alcoholics with active HCV infection develop cirrhosis and HCC more rapidly and in a higher frequency, than non-alcoholics who are HCV-actively infected.[15]

Therefore, the role of HBV and HCV infections in alcoholics with liver disease may be synergistic in causing severe chronic liver disease and even HCC.[16]

ETHANOL METABOLISM AND THE PATHOGENESIS OF ALCOHOLIC LIVER DISEASE

Ethanol metabolism in hepatocytes: Two enzyme systems, which reside in the hepatocyte, are the main participants, in the oxidative processes of ethanol metabolism: the cytosolic enzyme Alcohol Dehydrogenase (ADH), and an isoenzyme of cytochrome P450 the P4502E1, a component of the mixed function oxidase system. It resides, mainly, in the endoplasmic reticulum.

Oxidation of ethanol through the ADH pathway, produces acetaldehyde which is converted to acetate. Both reactions (Figure) reduce Nicotinamide Adenine Dinucleotide (NAD) to NADH. It is believed that excess NADH is responsible for a number of metabolic disorders identified in alcoholics (Table 1).[17]

Cytochrome P4502E1 normally represents a minor pathway of ethanol metabolism. It seems, however, to play an important role in ethanol oxidation in alcoholics who consume large amounts of alcohol. The induction of P4502E1 contributes to metabolic tolerance of ethanol in alcoholics and also affects the metabolism of other drugs, in that P4502E1 has the capacity to convert many foreign substances (industrial solvents, anesthetics, current medications) to toxic metabolities.[18]

Recent observations suggest that the induction of cytochrome P4502E1 by alcohol results: a) In enhanced oxidative stress (reactive oxygen species formation) in alcoholics, which in turn, results in the formation of hydrogen peroxide, as well as ethanol-derived hydroxyethyl-free radicals. It is believed that these reactive sub-

$$\text{Ethanol} + \text{NAD}^+ \xrightarrow[(\text{P4502E1})]{\text{ADH}} \text{Acetaldehyde} + \text{NADH} + \text{H}^+$$

$$\text{Acetaldehyde} + \text{NADH} + \text{H}^+ \xrightarrow{\text{ALDH}} \text{Acetate} + \text{NADH}$$

ALDH: Acetaldehyde Dehydrogenase

Figure. Both reactions result to the reduction of the redox state NAD/NADH, of the liver cell.

Table 1. Metabolic abnormalities due to increased ethanol metabolism in alcoholics

1. Hyperlactacidemia and lactic acidosis
2. Decreased urinary excretion of uric acid with secondary hyperuricemia
3. Reduced gluconeogenesis resulting in hypoglycemia
4. Increased levels of a-glycerophosphate with subsequent increased concentration of triglycerides in the liver cells
5. Inhibition of Krebs cycle
6. Inhibition of fatty-acid oxidation, hyperlipidemia and steatosis
7. Reduced protein synthesis
8. Increased collagen synthesis

stances are responsible for peroxidation of cellular lipids, which in turn generate highly reactive aldehydes.[19] b) May also contribute to vitamin A deficiency, by accelerating hepatic microsomal degradation of retinol and c) May activate carcinogens.[17]

The interactions of ethanol with other drugs and chemicals, through the induction of P2502E1 and other pathways, are subjects of current research and are not discussed in this review.[18]

The role of acetaldehyde overproduction in the pathogenesis of ALD: Under normal conditions ethanol-derived acetaldehyde is changed by oxidation to acetate. Under conditions of ethanol overconsumption however, the subsequent overproduction of acetaldehyde and the lowered ALDH activity in the liver cells result in increased levels of acetaldehyde in the hepatocytic environment. It is believed that the excess intrahepatic acetaldehyde, derived under conditions of alcoholism, exerts toxic effects which contribute to pathogenesis of ALD. These toxic effects can be summarized as follows:

a) acetaldehyde blocks the secretion of proteins by binding to the tubulin of microtubules. Retention of protein, lipid, water and electrolytes results in hepatocytic swelling, a characteristic feature of ALD.

b) it inhibits the activity of key enzymes and reduces the oxygen utilization in mitochondria.

c) it promotes cell death through depletion of glutathione, induction of lipid peroxidation and increases the toxic effect of free radicals and

d) it promotes the formation of acetaldehyde-protein adducts by binding to important proteins, such as collagen, albumin and lipoproteins. Such adducts may induce collagen production, may initiate the inflammatory process through cytokine release, or may act as neoantigens which stimulate immune responses.[17,20]

For reasons discussed elsewhere,[21,22] the toxic effects of acetaldehyde and of other aldehydes derived from the induction of P4502E1, seem to be enhanced at centrilobular zones of hepatic acini. This zonal predilection results in a more prominent centrilobular necroinflammatory process and an increased early perivenular fiboris, which are common pathological features in alcohol induced liver damage.

The role of nonparenchymal cells and endotoxins in the pathogenesis of ALD: There is evidence that nonparenchymal cells, i.e. Kupffer's cells, endothelial cells and fat-storing (Ito) cells, play an essential role in the initiation of necroinflammatory processes as well as in fibrogenesis. It is believed that perivenular fibrosis, a hallmark of alcohol-induced liver injury, is mediated by stimulated fat-storing cells. Under conditions of chronic alcoholism, fat-storing cells proliferate, are then depleted of their vitamin A content and finally, are transformed into "myofibrobasts" that start producing collagen and other intercellular matrix proteins. A high-fat diet may also be involved in fibrogenesis under these metabolic conditions.[23]

In addition, several studies suggest that chronic alcohol overconsumption predisposes to endotoxemia, which in turn aggravates alcoholic liver damage. Endotoxemia in alcocolics may be due to a combination of increased production of endotoxin from gut-derived bacteria, increased intestinal permeability and impaired detoxification of endotoxin by the reticuloendothelial system. There is experimental evidence that increased plasma endotoxin activates the Kupffer's cells to generate a variety of cytokines (i.e. interleukins and tumor necrosis factor); these substances may adversely affect the liver microcirculation and may promote the inflammatory process. Animal experiments showed recently that intestinal sterilization decreased plasma endotoxin and minimized the biochemical evidence of liver damage.[24]

In conclusion, the mechanisms of alcohol-induced liver disease seem to be fairly complicated and still uncertain. However, in recent years, attention has focused on the role of oxidative stress, the role of endotoxins and on the probable immunogenicity of aldehyde adducts.[18,25]

CLINICAL ASPECTS

Clinical features and biochemical findings are not specific for each of the clinical forms of ALD and the disease process seems to be best classified by using the histological changes. In this setting, the morphological spectrum of ALD includes fatty liver, with the fatty hepatocellular change as the main histological lesion producing clinical symptoms, alcoholic hepatitis, when clinical symptoms are associated with hepatocellular necrosis, inflammation and fibrosis on liver histology, hepatic fibrosis, when the disease is characterized mainly by profound portal and pericellular fibrosis, and finally cirrhosis, when fibrosis is associated with destruction of the normal lobular architecture of the liver and formation of regenerative nodules. These changes may develop as distinct entities, or their presence may overlap. In addition, chronic hepatitis and hepatocellular carcinoma (HCC) represent special clinical problems and are in-

cluded in this discussion.

Fatty liver: It is the most frequent form of ALD and may develop following consumption of large amounts of alcohol over a short period of time. Although clinical and biochemical abnormalities usually return rapidly to normal in patients who abstain from alcohol, the fat – mainly triglycerides- disappears within 2 to 6 weeks, depending on the severity of fatty changes. In individuals who continue to drink large amounts of alcohol, fatty liver may progress to alcoholic hepatitis and even to cirrhosis.[26]

The majority of patients with fatty liver remain asymptomatic, although a percentage usually complain of mild epigastric or right upper quadrant pain or of non-specific digestive symptoms such as anorexia, nausea and/or vomiting. Hepatomegaly and/or abnormal serum aminotransferases can be seen in a 30 to 50 percent of the cases. Marked intrahepatic cholestasis may be the predominant symptom in a number of patients. Rarely, the condition may be complicated by hyperlipidemia, haemolytic anaemia and jaundice (Zieve's syndrome). Hepatocellular failure is rare. Portal hypertention with splenomegaly and ascites can be observed in a small minority of patients. The most common biochemical abnormalities include increased aminotransferases, increased γGT, abnormal levels of serum bilirubin (in 20 to 30 per cent of the cases) and Alk. phosphatase (in almost 50 per cent of the cases), hyperlipidemia and less frequently anemia, thrombocytopenia, macrocytosis and prolonged prothrombin time. Significant increase of serum transaminases and decrease of prothrombin activity in a patient with fatty liver indicate the evolution of the fatty changes to steatohepatitis or to alcoholic hepatitis.[27]

On histology, fatty changes may range from vacuolation of a few hepatocytes to severe involvement of all the liver tissue. Steatosis is usually more prominent in centrilobular areas. The fat droplets may vary in size from small (microvesicular) to large (macrovesicular) droplets, the latter being more common. In a small number of cases microvesicular accumulation of fat is more prominent in perivenular areas, where the liver cells have a foamy appearance and may be associated with intrahepatic cholestasis, focal necrosis and increased perivenular collagen deposition. Megamitochondria can be seen as small rounded eosinophilic inclusions in hepatocytes with foamy degenerative changes.[28]

Fatty liver is not pathognomonic for chronic alcoholism. It can be seen in a number of other conditions including obesity, diabetes mellitus, intestinal by-pass surgery, severe malnutrition and exposure to toxins. Foamy degenerative changes of hepatocytes are also seen in fatty liver in pregnancy and in Reye's syndrome, conditions of exceptional severity and high mortality.[29]

Alcoholic hepatitis: Alcoholic hepatitis develops only in a small proportion of alcoholics even after heavy drinking for many years. It has been recognized as a precirrhotic lesion, although it's natural history is not fully understood. The clinical evolution of alcoholic hepatitis depends on several factors including future drinking behaviour, the sex of the patient and the severity of the initial lesions on liver biopsy. Although abstinence from alcohol does not guarantee regression of the histologic lesions, yet such a regression can be observed only in patients who finally abstain from alcohol. In patients who continue to abuse alcohol, in women and in individuals with severe alcoholic hepatitis on the initial liver biopsy, the disease usually progress to cirrhosis. Approximately 30 to 40 percent of patients with moderate or severe alcoholic hepatitis finally develop alcoholic cirrhosis.[27]

On liver histology, alcoholic hepatitis is characterized by the presence of the following lesions:

1) **Degenerative hepatocellular changes** in the form of "ballooning" degeneration. Affected hepatocytes show an hydropic finely granular cytoplasm and may contain Mallory's hyaline bodies. These are eosinophillic aggregates of a dense proteinaseous material which usually encircles the nucleus of the necrotic hepatocytes.

2) **Intalobular inflammatory infiltrates** consisting mainly of neutrophils, at least in the early stages of the inflammatory process. Lymphoid cells may predominate in the course of the disease later. Mallory bodies surrounded by polymorphonuclear cells, though not pathognomonic, are indicative of alcoholic hepatitis.

3) **Increased collagen deposition** which results in pericellular (perisinusoidal) and/or perivenular fibrosis. Severe alcoholic hepatitis may result in extensive centrolobular fibrous scars. Fibrous bridges may subsequently develop and link these areas to adjacent fibrotic portal tracts.

   Perivenular fibrosis, however, may be observed without any other histological feature of alcoholic hepatitis, except probably microvesicular fatty changes in centrilobular areas. In such cases these histological lesions may represent residual changes of a previous alcoholic hepatitis or precursors of alcoholic cirrhosis.[28]

Furthermore, dense fibrosis of perivenular regions may narrow or occlude the lumens of the terminal hepatic veins, resulting in portal hypertension. The term "chronic sclerosing hyaline necrosis" has been used to describe this progressive centrilobular destructive process[30] and

4) Other lesions, such as fatty changes, lipogranulomas, megamitochondria and intrahepatic cholestasis (especially in severe forms of the disease).

It must be pointed out that all the above described changes can be considered as diagnostic but not as pathognomonic for alcoholic hepatitis. Mallory bodies with neutrophillic infiltration and fibrosis may be found in diseases associated with chronic cholestasis such as Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis and Wilson's disease. Mallory's hyaline may also be observed in a number of other disorders such as hepatocellular carcinoma, Indian childhood cirrhosis and abetalipoproteinaemia. In these conditions hyaline degenerative changes are more prominent in periportal regions.[31]

The clinical presentation of alcoholic hepatitis varies from a mild illness to a severe or fulminant hepatitis with jaundice, ascites, variceal bleeding and encephalopathy. The severity of clinical signs and symptoms depends on the severity of the histological changes on liver biopsy. Approximately 60 percent of patients with mild to moderate alcoholic hepatitis on liver biopsy, present with non-specific symptoms such as anorexia, nausea, fatigue, lethargy or diffuse abdominal pain. Some 10 to 15 percent of patients will present with jaundice. The most common physical finding is hepatomegaly ranging from mild enlargement to massive expansion of the liver into the pelvis. Many patients exhibit hepatic tenderness and may have an audible bruit over the area of the liver. 20 to 30 percent of patients develop splenomegaly. Fever may be one of the prominent features in 45 to 50 percent of patients. Approximately 50 percent of individuals with moderate to severe disease are jaundiced and some 40 percent develop ascites. A percentage of severely ill patients may present with symptoms of varying degrees of hepatic encephalopathy. In addition, spider naevi, cutaneous telangiectasias, and palmar erythema are usually present. Parotid enlargement, gynaecomastia and testicular atrophy are present in a 10 to 20 percent of patients.[3]

Laboratory test results (Table 2) are not diagnostic for alcoholic hepatitis, especially in cases of mild disease. Serum gammaglutamyltranspeptidase and Aspartate aminotransferase are invariably raised. Nevertheless AST rarely exceeds the level of 300 U and ALT is usually slightly elevated, even in cases with severe hepatocellular necrosis. Leucocytosis is usually present in 25 to 95 percent of cases and correlates with the severity of the disease.

Table 2. Alcoholic hepatitis: Abnormal laboratory test results

1. Hematocrit <37%	70%
2. WBC over 10,000/mm^3	45%
3. AST	
<500 U	99%
<300 U	95%
<50 U	20%
4. Serum Alk. Phosphatase 3 – fold over normal	70%
5. Serum bilirubin over 1,0 mg/dl	75%

Although the combination of jaundice, fever, tender hepatomegaly and leucocytosis in an acutely ill patient with a history of alcohol abuse leads to the being most probable diagnosis of alcoholic hepatitis yet a number of other conditions, such as hepatic abscesses, biliary tract disease or even hepatocellular carcinoma have to be excluded. Ultrasonography, CT scan and of course a liver biopsy, whenever it is permissible, usually help to avoid diagnostic errors.[3,32]

The short-term prognosis of alcoholic hepatitis depends of the severity of hepatic lesions in liver biopsy and the presence or not of cirrhosis. Clinical and laboratory parameters indicating severe disease and a high risk of acute mortality include: (a) the presence of "spontaneous" encephalopathy, (b) marked prolongation of prothrombin time, (c) serum bilirubin more than 25 mg/dl, (d) marked hypoalbuminaemia with or without ascites and (e) increased serum creatinine. Under such circumstances almost 50 percent of patients with severe alcoholic hepatitis die during the first thirty days of the initial hospitalization. Patients with severe alcoholic hepatitis who have recovered from the acute illness, seem to be at extremely high risk of acute mortality after only a brief relapse into alcohol abuse.[32]

Alcoholic fibrosis: Hepatic fibrosis without changes of hepatitis or cirrhosis in liver biopsy is not widely recognized as a clinical entity caused by alcohol. The incidence of hepatic fibrosis has been found to be high in Japan where alcoholic hepatitis is rare.

Histologically it is characterized by pericellular and perivenular fibrosis, thickening of terminal hepatic venules and absence of changes of alcoholic hepatitis and

cirrhosis.

Clinical features are mild. Most of the patients have hepatomegaly, some 30 percent of them have abdominal discomfort and a few have mild jaundice and elevation of aminotransferases. Alcoholic fibrosis has been considered as a precusor of cirrhosis.[33]

Chronic Active Hepatitis: Histological changes of chronic hepatitis (active or persistent) are occasionally seen in the liver of alcholics. The role of alcohol in the etiology of these lesions has not been definitely established and chronic hepatitis has not been recognized as an alcohol-related pathological lesion by several investigators. An increased prevalence, however, of hepatitis B and C viral infections in alcoholics may be implicated in the development of this clinicopathological entity. A possible concomitant or synergistic role of hepatitis B and C viruses in the progression of ALD may exist and has already been discussed at the beginning of this review.

Besides the pathogenetic mechanisms, the diagnosis of alcohol-induced chronic active hepatitis may be established on a clinical basis when the following criteria are fulfilled: (a) when other causes of chronic hepatitis, such as hepatitis B and C viruses, drugs, autoimmune reaction or metabolic disorders can be excluded, (b) when the liver histology is compatible with chronic active hepatitis and there are no lesions of alcoholic liver disease and (c) when clinical and histological improvement is achieved after alcohol withdrawal.[34]

Alcoholic Cirrhosis: Cirrhosis is the final stage of ALD and it is believed to develop in only a minority of alcoholics. It is initially micronodular. As the condition evolves, however, particularly with abstinence from alcohol, the nodules become larger and irregular in size and the histological picture takes the form of a macronodular cirrhosis. In patients who continue to drink, fatty changes and acute inflammatory lesions of alcoholic hepatitis may be seen in the regenerating nodules.[30]

The clinical spectrum of alcoholic cirrhosis varies from an anicteric, asymptomatic hepatomegaly to an overt hepatocellular failure with portal hypertention. Cirrhotic patients who have stopped drinking for years, usually present with an incidental finding of hepatomegaly and/or increased levels of serum animotransferases during a routine clinical examination or sometimes with one of the major complications of cirrhosis such as ascites or variceal bleeding. Well-compensated cirrhosis may give no symptoms at all, or patients may present with minor symptoms, such as anorexia, malaise or early fatigability. In contrast, cirrhotic patients who continue to consume large amounts of alcohol, usually present with symptoms of hepatic decompensation such as jaundice, ascites, peripheral oedema and gastrointestinal haemorrhage, probably because of a superimposed alcoholic hepatitis.

Hepatomegaly is the most common physical sign. The liver is usually moderately enlarged, firm and has an irregular surface. The spleen is palpable in some 25 percent of patients. Other features of portal hypertention (varices, collateral veins in the abdominal wall) are usually present in 60 to 70 percent of patients. Jaundice is observed in one third of patients and ascites in 30 to 40 percent. Right-sided cirrhotic hydrothorax can be observed occasionally. Features of hepatic encephalopathy (flapping, cerebral dysfunction etc) may be present in up to one-third of patients. Hepatic stigmata (spider naevi, cutaneous telangiectasia, palmar erythema etc) are frequently observed and although not specific, are usually more profound and fairly dignostic for alcoholic cirrhosis.[27,32]

The prognosis depends on two basic parameters: drinking behavior and the presence of complications. For patients who remain abstinent from alcohol and have not developed complications, the 5-year survival rates usually exceed 90 percent. In contrast, the 5-year survival rate is reduced to 50 or 60 percent for patients who present with complications of a decompensated cirrhosis.[35]

The condition, however, that affects significantly the survival of patients with alcoholic cirrhosis is the development of Hepatocellular Carcinoma (HCC); the majority of these patients die within weeks or months of diagnosis.

According to recent epidemiological studies, 5 to 15 percent of patients with alcoholic cirrhosis in USA and some 20 percent in Europe, develop HCC. Although it is quite clear that chronic alcoholism seems to be a major causative factor in the development of HCC, especially in the areas of the world with low incidence of hepatitis B and C viral infections, yet the exact relationship between alcohol – cirrhosis – HCC, the role of HBV and HCV infections in alcoholics with HCC and the possible carcinogenic effects of alcohol on the initiation and promotion of hepatic carcinogenesis, are not fully understood.

The role of hepatitis B and C viruses in the evolution of ALD and their possible carcinogenic effects have already been discussed and are topics of current investigations.

On the other hand, the fact that chronic alcoholism-associated HCC is growing almost exclusively in the cirrhotic liver, favors the histologically proved evolution of carcinogenesis in the order of micronodular cirrhosis leads to macronodular cirrhosis which in turn exhibits precancerous dysplastic nodules leading to neoplastic nodules.[36]

Regarding the possible carcinogenic effects of ethanol, it is believed that although ethanol per se seems not to be carcinogenic, yet it seems possible that it acts as a cocarcinogenic substance at different body sites, with a variety of chemical carcinogens. The proposed mechanisms by which ethanol excerts its cocarcinogenic effects include: (a) Induction of microsomal enzymes which activate procarcinogens, (b) interference with the capacity of cells to repair carcinogen-induced DNA damage, (c) alteration of immune responsiveness, (d) exacerbation of dietary deficiency and (e) excerting its solvent effects on various carcinogens and allowing them to penetrate the target tissues more easily. These mechanisms are extensively analyzed in several comprehensive reviews.[137,38]

TREATMENT OF ALCOHOLIC HEPATITIS AND CIRRHOSIS

Abstinence from alcohol, nutritional support, bed rest and corticosteroids treatment (for selected patients with severe alcoholic hepatitis) are the main therapeutic approaches, which are currently accepted for severe ALD.

Abstinence is the mainstay for any treatment. It seems to be difficult, however, for many patients to achieve a permanent abstinence from alcohol without of psychiatric support. A recently published meta-analysis for use of pharmacological agents for alcohol withdrawal, showed that benzodiazepines are the most effective regimens among sedative-hypnotic medications, in helping alcoholics to achieve a definite abstinence from alcohol.[39]

Furthermore, there is evidence, that endogenous opioids are involved in modulating the craving of alcohol. Naltrexone is a pure opioid antagonst; recent studies have shown that naltrexone effectively reduces the rate of relapse to alcoholism.[40]

As has already been mentioned, the presence of malnutrition and vitamin deficiencies, in cases with severe ALD, is well established.

Hyperalimentation, although not proved, seems to have positive therapeutic results for patients with alcoholic hepatitis. Indeed, a high calorie – high protein diet (with or without anabolic steroids) seems to be one of the most important things to do in moderately or severely malnourished patients. There is evidence that positive nutritional balance is associated with clinical and biochemical improvement of the disease and enhanced modilization of fat from the damaged liver. In addition, recent studies[41] have shown that a diet enriched in saturated (but not in polyunsaturated) fatty acids and vitamin E, effectively reduces the liver damage, at least in animals, by decreasing lipid peroxidation.

Since endotoxemia seems to play a fairly important role in the pathogenesis of ALD, it seems reasonable to assume that intestinal sterilization with antibiotics may prevent alcohol-induced liver damage.[24]

The beneficial effects of corticosteroids in alcoholic hepatitis have been studied extensively during the last two decades. The results of several (twelve or more) randomized, placebo-controlled trials and two meta-analyses, support the concept that corticosteroid treatment affects positively the short-term survival of patients with severe alcoholic hepatitis and spontaneous encephalopathy. These results have been confirmed by a recent study[42] that showed, for the first time, that survival benefit from corticosteroid treatment persisted for 1 year after therapy. Beneficial effects of corticosteoids were found in this study to be more profound in patients with marked polymorphonuclear infiltrates of the liver and high serum leukocyte counts.

Patients with gastrointestinal haemorrhage, infections, or hepatorenal syndrome should be excluded from treatment with corticosteroids. According to current policy, corticosteroid treatment is not recommended for the routine management of alcoholic hepatitis or decompensated cirrhosis.

Anabolic steroids to remove fat, colhicine and penicillamine to prevent hepatic fibrogenesis, and propylthiouracil to decrease perivenular hypoxia, have also been tried in a limited number of therapeutic trials. Data concerning the real usefulness of these therapeutic modalities are still inadequate and controversial.

Liver transplantation can be considered if there is evidence of progressive liver failure despite medical treatment and despite abstinence from alcohol. The most suitable candidates are probably patients with end-stage liver disease, with features of portal hypertention, episodes of spontaneous bacterial peritonitis, recurrent episodes of hepatic encephalopathy or variceal bleeding and with abstinence from alcohol for 6 or more months. It has been shown that liver transplantation in patients with end-stage

ALD is associated with a 5-year survival in approximately 70 percent of the cases. These results do not differ substantially from those reported for patients with non-alcoholic liver disease.[43]

The proportion of patients who return to alcohol consumption following transplantation, varies from series to series and seems to reflect the drinking behaviour prior to transplantation. Thus, according to recent studies,[44] the recidivism rate in patients who have been abstinent for 6 or more months prior to transplantation is very low, while the recidivism rate for individuals drinking up to the time of surgery is usually in excess of 60 percent.

Compliance with follow-up and medication after transplantation has been reported as satisfactory. In addition, there is evidence that the incidence of rejection is low in patients transplanted for ALD, especially for those who continue to drink.[45]

Finally, available data confirm that the quality of life for recipient survivors seems to be excellent.[46]

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