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EDITORIAL

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Alcoholic liver diseases: current review

By the term Alcohol-induced Hepatic Diseases [ALD] we refer to the hepatopathy induced by ethanol and/or its metabolites. The study of this subject is of great importance since it represents a prototype of disease in which biological, clinical, epidemiological, sociological and psychological factors converge.

Unlike many other diseases, ALD can be avoided, as long as the ingestion of ethanol does not exceed certain limits, and it remains static or even regresses after alcoholic abstinence (16).

ALD is very common, [it is often the most common type of chronic liver disease] in almost every country, including Brazil. This fact is related to the high consumption of ethanol, the lack of effective therapies, and the difficulty the majority of alcoholics have remaining abstinent.

Up until about 30 years ago, it was still thought that hepatic diseases and other important pathological conditions observed in alcoholics were exclusively consequences of the associated nutritional deficiencies and not to the toxic effects of alcohol. This theory was based mainly on the work of Best et al. (2). The authors concluded that ethanol was as damaging to hepatic cells as sugar was, in other words, that it was not hepatotoxic.

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The hepatic alterations so frequently found in alcoholics were considered to be principally due to the deficiency of lipotropic substances, such as choline and methionine, in spite of the fact that in this research, done on rats, the ethanol consumed was only 10-20% of the total calories of their diet. This dosage resulted in very low levels of ethanolemia [thus not representing the habitual ethanol consumption of alcoholic patients] Studies developed over recent years made it possible to show that even with an adequate diet, and without nutritional deficiency, ethanol can produce steatosis, ultrastructural alterations [in the mitochondrion, endoplasmatic reticulum, and plasmatic membranes] and discrete fibrosis in rats (3), fibrosis and cirrhosis in baboon monkeys (6) and steatosis in man (8). Epidemiological data also reinforce the arguments as to the hepatotoxity of ethanol. A marked reduction occurred in the mortality rate of cirrhosis in the United States during the Prohibition, when alcohol consumption was outlawed, and in France, during the Second World War, when there was wine rationing. These indexes began to climb after the liberation of alcoholic sales. In a recent epidemiological study it was observed that the reduction of the mortality rates due to cirrhosis was related to the reduction in the per capita consumption of alcohol and the increase in the number of members of Alcoholics Anonymous (10). The death rate for cirrhosis in the United States has diminished in the last decade, partially due to the treatment of alcoholism and the important work done by Alcoholics Anonymous (24). A recent study on the population of the United States noted that the percentage of cirrhotics was significantly greater in those that had three drinks per day than in those that abstained. The results of all these studies, considered together, allow us to confirm that ethanol is truly a hepatotoxic substance. There are, nonetheless, rare

differing opinions. Derr et al. [4] deny the toxic nature of ethanol and affirm that "experimental data do not demonstrate, to this day, that ethanol is, in itself, a hepatotoxic". And they even assure that ethanol "allows or favors recovery from hepatic disease". This concept has no scientific basis, is based on incomplete and distorted analysis of clinical and experimental studies, and besides this, constitutes a disservice to those who, at the cost of great sacrifice, are in abstinence (7).

In the study on rats done by Derr et al. (4) the quantity of ethanol administered represented only 26% of the total energy consumed and the levels of ethanolemia were low.

Ethyl alcohol, being a liposoluble substance, can compromise the structure and function of membranes, modifying the resistance of the cell and the organelles to aggressions and physiological signalling. The pathogenesis of AHD is intimately related to the metabolism of ethanol, which is processed predominantly in the liver, the organ which contains the greatest quantity of enzymes capable of metabolizing that substance. It has been demonstrated that a significant fraction of alcohol ingested in "social" doses is oxidated in the stomach as well, which possesses the enzyme alcohol dehydrogenase (ADH). The magnitude of this process of oxidation in the stomach can influence the bioavailability of the ethanol and modulate its potential toxicity. The gastric activity of ADH is less in women than in men. This factor could contribute to a greater vulnerability to the effects of ethanol in females. Recently various isoenzymes of gastric ADH were identified as well as genes that corresponded to the different kinetic properties of those same enzymes. An interesting aspect observed in 80% of Japanese patients was the absence of an ADH gastric isoenzyme. Could the absence of this enzyme be eventually linked to the greater incidence of gastric cancer in Japanese people?

In the hepatocyte there are three principal pathways of metabolization, each one of which is located in a different compartment of that cell: via ADH, in the cytosol or soluble fraction; microsomic ethanol oxidation system [MEOS], located in the endoplastic reticulum, and the catalase in the peroxisomes and mitochondria. The most important pathway of ethanol oxidation is mediated by the ADH. Currently we know that there are various molecular forms of ADH in the human liver with different activities, or rather, that display different elimination coefficients. MEOS is a dependent cytochrome P-450; it has been demonstrated that the chronic consumption of alcohol causes induction of a specific cytochrome P-450, [P-450 2E1] which shows greater activity than others oxidating ethanol, carcinogens, and drugs like paracetamol. Its been shown that there is genetic polymorphism of the cytochrome P-450 2E1, a condition that could contribute to explain the differences of susceptibility that alcoholics show to the adverse effects of alcohol.

The metabolism of ethanol is performed in two phases. In the first it is transformed into acetaldehyde, and in the second it is converted into acetate. Currently we know that acetaldehyde is a toxic substance capable of affecting the liver and various sectors of the organism. The cofactors NAD and NADH participate in oxidation of ethanol, respectively, when it is processed via ADH and MEOS. The oxidation of the acetaldehyde is effectuated with the participation of the enzyme aldehyde dehydrogenase [ALDH], acting as a cofactor NAD. With respect to ALDH, isoenzymes were also identified, since ALDH2 displays a very low elimination coefficient. The reddening or blushing of the skin, commonly observed in Orientals after ingestion of alcohol, would be caused by the association of ADH2 [of high activity] and of ALDH2 (low activity) The activity of ALDH (like that of ADH) can diminish after hepatic damage.

As a result of the oxidation of the ethanol there is an increase in the NADH/NAD ratio, the formation of acetaldehyde (which is elevated in alcoholics) and microsomal proliferation in the hepatocytes, after chronic consumption of ethanol. As a consequence of the greater production of NADH there will be: alterations in the metabolism of the lipids, carbon hydrates and uric acid, a reduction in protein synthesis and an increase in collagen and steatosis. The formation of acetaldehyde will result in: covalent linkage in proteins, an increase in collagen synthesis, mitochondrial dysfunction and alteration of the cellular membrane. The microsomal proliferation in the hepatocyte can cause: peroxidation of lipids, hypoxia and a hypermetabolic state, acceleration of the metabolism of drugs, acceleration of the metabolism of ethanol, an increase in the levels of acetaldehyde, activation of hepatotoxic agents and carcinogens, and an increase in the degradation of vitamin A and testosterone.

Current knowledge about hepatic damage in AHD allows us to affirm that this can occur through various mechanisms, the following of which are mentioned in the literature: alterations of the membrane by the ethanol, an increase in the NADH/NAD ratio, formation of acetaldehyde, microsomal proliferation in the hepatocyte, alterations in the mitochondria, retention of proteins and water in the hepatocyte, hypermetabolic state, increase in fatty deposits, immunological alterations, formation of fibrosis, effects of cytokines, and malnutrition, as an aggravating and predisposing factor.

The risk factors for AHD are: amount of ethanol ingested, duration [months-years] of ingestion, continuity, female sex, genetic factors and malnutrition (13). Although normally large doses of ethanol (160 grams or more per

day) are needed to induce hepatitis or cirrhosis, men can sometimes develop significant AHD with only 40g/day and women with 20g/day. Cirrhosis develops generally after 10 or more years of ethanol consumption. The continuity favors the formation and progression of AHD, since it impedes liver regeneration. The genetic factor is important, the presence of ADH being related with the subtype cytochrome P-450 2E1 in the liver, among other aspects. It is worth remembering that hepatotoxic substances other than ethanol can be present in national brands of white rum ("pinga") (15) and is sometimes capable of augmenting the effects of ethanol.

The principal hepatic lesions from ethanol are: steatosis, alcoholic hepatitis, hepatic cirrhosis, perivenular fibrosis, and, less frequently found, active chronic hepatitis [23]. Some authors mention that ethanol favors the development of hepatocarcinoma, especially in patients with cirrhosis (17). Steatosis is the most frequent hepatopathy of alcoholic etiology found, being considered a condition that predisposes one to alcoholic hepatitis. Steatosis can be associated with perivenular fibrosis, alcoholic hepatitis, active chronic hepatitis, or cirrhosis. Until recently, steatosis was considered a benign lesion. Currently some authors include steatosis among the pre-cirrhotic lesions since it can evolve to perivenular fibrosis and subsequent progression to cirrhosis. Though rarely, steatosis sometimes can be the cause of sudden death. Alcoholic hepatitis is responsible for high death rates, being, as determined a pre-cirrhotic lesion. Cirrhosis is considered the irreversible phase in AHD. Some authors, however, report reversibility of this lesion (5). Alcoholics can display non-alcoholic hepatopathies [acute or chronic hepatitis of viral etiology, cholangitis, accumulation of iron or copper or other causes]. There is a higher prevalence of hepatitis viruses B and C in alcoholics than in healthy subjects (14,18). We do not know to what extent these agents are involved in the pathogenesis of AHD. In any case, the prognosis for acute and chronic viral hepatitis is worse in alcoholic patients. The chronic viral infection also elevates the risk of the development of hepatocellular carcinoma in AHD patients.

The diagnostic study of AHD should be based on anamnesis, on physical examination, laboratory exams, image producing diagnostic methods, histological exams and marked response to alcohol abstention. The symptoms of AHD patients are non-specific. Knowledge of the drinking habits is of great importance, keeping in mind that alcoholics often underestimate their ingestion. In the physical exam they may or may not display signs related to alcoholism and/or hepatic disease, such as: vascular spiders, jaundice, gynecomasty, palmar erythema, and hepatosplenomegaly, among others. The principal laboratory exams are: indexes of aspartate aminotransferase [AST]/ alanine aminotransferase [ALT], gamma glutamyl transferase [GGT]/ alkaline phosphatase, determinations of levels of albuminemia, of prothrombin time, and of bilirubinemia. AST/ALT equal to or greater than 2 is very suggestive of alcoholic hepatitis or cirrhosis. This is a test of low sensitivity, but of relatively high specificity. The GGT is elevated in a considerable number of AHD patients but may also be high in alcoholics without evident hepatopathies. This enzyme may be diminished during pregnancy, and therefore during this condition it is not useful in a diagnostic study of excessive consumption of alcohol. The GGT is more elevated than the alkaline phosphatase in patients with AHD. The determinations of the levels of albuminemia, of prothrombin time, and of bilirubinemia are useful for detecting liver dysfunction. These biochemical tests, though useful for the diagnostic study of AHD, are not specific. There are tests to study hepatic fibrogenisis in the serum and they would be applicable in relation to AHD . The determination of the seric peptides of the procollagen type III can be useful for the diagnosis of intense alcoholic hepatitis (12) and, the seric and hepatic determinations of the collagen type IV are useful in distinguishing between alcoholic and non-alcoholic hepatopathy (26). The importance of these and other existing tests for the diagnosis of AHD needs further evaluation.

The new, non-invasive techniques of image diagnosis are useful for the study of hepatopathies in general. Recently some authors described, for the first time, ultrasonography images that delineated pseudo-signals of the parallel channels, which allows the possibility of diagnosing acute alcoholic hepatitis (25). An ultrasonography can also supply data that can suggest the existence of steatosis, cirrhosis, and portal hypertension, and enable the diagnostic differentiation between intrahepatic cholestasis [sometimes present in alcoholic hepatitis], and extrahepatic cholestasis, as well as other useful information. The computerized tomography, an exam currently simplified by the advent of the spiral type, can supply images suggestive of steatosis, cirrhosis (including aspects characteristic of the advanced phases of this lesion), through the presence of confluent hepatic fibrosis (19), of portal hypertension through the presence of gastric varices, and of tumor. Magnetic resonance, besides enabling the diagnostic differentiation between primary biliary cirrhosis and alcoholic cirrhosis, can supply images that are statistically associated with the presence of portal and lobular necrosis and portal inflammation (11). In spite of the importance of laboratory tests and image producing techniques for diagnosis, a more definitive diagnosis of AHD, the type of lesion and activity, can

only be established with the inclusion of the morphological data supplied by laparoscopy and biopsy. We should note, however, that a morphological study without knowledge of the clinical data does not allow a diagnosis of the alcoholic etiology of the hepatic disease. Besides this, the histological exam does not tell us about hepatic dysfunction, and so cannot substitute for the designated tests for hepatic function. On the other hand, we should mention that frequently the hepatic biopsy is not performed for various reasons, among which are disturbances of the hemostasis and refusal of the patients to undergo this exam. As for the morphological aspects, we are reminded that steatosis is commonly of a macrogoticular pattern. The morphological findings of alcoholic hepatitis considered essential are: degeneration and necrosis, inflammatory infiltrate (predominantly of neutrophils and fibrosis), which are visualized in the centrilobular zone, as long as there is no cirrhosis. Alcoholic hepatitis can be classified as minimum, diffuse, and advanced. From the histological point of view, it's not possible to establish the limit between acute and chronic alcoholic hepatitis. The histological alterations are not pathognomonic since they can be found in patients with diabetes and pre-diabetes, obesity, hepatoma, Wilson's syndrome, cirrhosis from infancy in India, in patients undergoing parenteral nutrition, in patients taking medications [perhexiline maleate, amiodarone, glucocorticoids, estrogens], in patients with hyperlipemia and among those submitted to a jejunoileal derivation, gastroplasty or intestinal excision. The morphological pattern of the initial phases of cirrhosis is micronodular. With the evolution of the lesion and especially after a period of abstention of ethanol the pattern could be macronodular or mixed. In cirrhosis the following elements are diffusely present: fibrosis, formation of nodes of hepatocytes, frequently with evidence of regeneration and distortion of the lobular architecture.

One aspect of great interest for the diagnosis of AHD is a marked improvement, both clinical and laboratorial, that appears after alcohol abstention. However, the absence of this improvement does not allow exclusion of the hypothesis of AHD.

The treatment of AHD includes common general measures and the use of medication. Total alcohol abstention generally improves the prognosis of steatosis, alcoholic hepatitis, periveniular fibrosis, cirrhosis [particularly when there are no esophagogastric varices] and active chronic hepatitis. The correction of the hydroelectrolytic and metabolic disturbances, of proteiu-caloric malnutrition and vitamin deficiencies is of great importance. In the same way care should be taken with reference to the retention of liquids, renal dysfunction, digestive hemorrhagic infections and hepatic encephalopathy. Recently there have been studies which verified the utility of some drugs in the treatment of AHD. Corticosteroids are efficient in the treatment of patients with the intense form of alcoholic hepatitis, especially when there is hepatic encephalopathy without systematic infection, renal insufficiency and/or gastrointestinal bleeding requiring blood transfusions (22). The use of colchicine may be capable of extending the life span of cirrhotics, since it could provide a histological and clinical improvement (5). There is, however, the need for multicentric studies to confirm the efficiency of this drug. Ursodeoxycholic acid seems to have hepatoprotective properties, being really efficient in the treatment of light or moderate intrahepatic cholestasis.

S-adenosyl-L methionine is useful in the treatment of AHD, especially when there is intrahepatic cholestasis (20). Phosphatidylcholine, the main component of the extract of polyunsaturated lecithin from soy beans, will probably be useful in the treatment of AHD, as its use in baboon prevented the development of septal fibrosis and cirrhosis (9). With regard to liver transplants, they should be considered for cirrhotics when there is a progressive hepatic insufficiency in spite of adequate medical treatment, especially in alcoholics who are in abstinence for at least three months.

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