Chapter

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Alcoholic Liver Disease (ALD)

SABYASACHI RAY

INTRODUCTION

Liver disease related to alcohol (Ethanol, ethyl alcohol) is very common global problem and is one of the major medical complications of alcohol abuse. Daily consumption is usual for causation of liver disease. Intake of alcohol is measured as one unit. Each unit contains 8 gm of ethanol and variable in various common beverages, e.g. 1/2 pint of beer, 1 measure of spirit, 1 glass wine or sherry. Risk depends on amount and frequency: high risk–160 gm/day, moderate–80 gm/day, low–40 gm/day. One unit is eliminated every hour, so spread drinking with food delays absorption and keeps lower blood level of alcohol. The absorption of alcohol is lower when consuming low concentration beverages such as beer compared with high concentration spirits. Apart from liver and pancreas, alcohol affects multiple organs, CNS, muscles, CVS, GI, metabolic, endocrine, blood, bone. Safe limit for alcohol consumption remains controversial. However, Royal College of Physicians, UK guidelines mentioned 21 units/week for men and 14 units/week for women.

CLASSIFICATION

The liver injury after acute alcohol consumption is classified as:

1. ***Alcoholic fatty change (Steatosis)***: May be reversible after abstinence.
2. ***Acute alcoholic hepatitis:*** Develops due to large amount of alcohol for a long period and the outcome may range from abnormal liver functions with no symptoms to hepatic encephalopathy.
3. ***Cirrhosis:*** When liver structure is significantly damaged, normal liver cells are replaced by fibrosis and nodules, cirrhosis ensues. Exact mechanism for development of acute hepatitis or cirrhosis is not known.
4. ***End-stage alcoholic liver disease:*** Death occurs due to hepatic encephalopathy, profuse GI bleeding, overwhelming infections, renal failure and hepatocellular carcinoma.

EPIDEMIOLOGY

Factors Related to Prevalence

- Affinity for alcohol
- Availability
- Social acceptability
- Concomitant use of other hepatotoxic agents.

The World Health Organization (WHO) estimates that 140 million people worldwide suffer from alcohol dependency, causing damage to lives and economies. In Europe, approximately one in four deaths among men aged 15-29 is alcohol-related. People with acute alcohol intoxication are often encountered in hospital emergency departments, and the burden placed on emergency and out-patient services by this patient group is enormous. Although acute intoxication is not the main cause of alcohol-related deaths, it is the major factor contributing to premature death.

Key Points

- WHO estimates that 140 million people worldwide suffer from alcohol dependency, causing damage to lives and economies.

- Mortality due to cirrhosis is higher in countries with a higher per capita consumption of alcohol.
- A daily intake of more than 60 grams of alcohol in men and 20 grams in women significantly increases the risk of cirrhosis.
- In addition, steady daily drinking, as compared with binge drinking, appears to be more harmful[1]
- Persistent and heavy for long period more risky than sporadic heavy drinking.
- In Europe, approximately one in four deaths among men aged 15–29 is alcohol-related.
- The risk of liver disease is more if large quantity is taken for a long duration[1]. Amongst heavy drinkers, 1/5th will develop alcoholic hepatitis and 1/4th cirrhosis[1].
- In USA , 2nd leading cause for liver transplantation is alcoholic cirrhosis.
- In UK alcohol accounts for 80% of all liver cirrhosis cases seen in district general hospitals and approximately 300,000 people are affected.
- Japan and India were previously of low prevalence. Recently alcoholic cirrhosis is gradually increasingly.
- In Italy the risk threshold for developing ALD was found to be 30 gm ethanol/day[2].
- A study in Denmark showed that 7-14 units consumption in women and 14-27 units consumption in men increased the risk of ALD[3].
- Women had greater susceptibility to ALD at any given level of intake.
- Men and women have equivalent alcohol elimination rates[4].

ALD is more likely if:

- Alcohol consumption daily for long
- Drinking without taking food
- High concentration drinks
- Mixing multiple alcoholic drinks
- Alcohol binge
- Women factors.

PATHOGENESIS

After consumption, alcohol is mainly metabolised within hepatic parenchyma and also in GI tract. Inside the liver cells alcohol is converted by alcohol dehydrogenase and cytochrome p450 2E1 to acetaldehyde, which is metabolised to **Acetate** by mitochondrial enzyme acetaldehyde dehydrogenase[4].

Events Causing Liver Damage

- Nicotinamide—Adenine Dinucleotide (NAD) is reduced to NADH By Alcohol dehydrogenase and acetaldehyde dehydrogenase
- Changed ratio of NAD/NADH causes fatty liver through inhibition of gluconeogenesis and fatty acid oxidation.
- If alcohol is taken for a long period, Cytochrome p450 2E1 gets up-regulated, causes oxidation of nicotinamide-adenine dinucleotide phosphate (reduced) (NADPH) to NADP generating free radicals[5].
- Hepatic macrophages are activated in chronic alcohol takers which subsequently produce TNF α (Tumor necrosis factor)[6].
- TNF α induces mitochondria to increase production of reactive oxygen species.
- Necrosis and apoptosis of liver cells is caused by oxidative stress. Due to deficiency of glutathione and vitamin E necrosis/apoptosis exaggerated.

  Free radicals initiate lipid peroxidation, which causes inflammation and fibrosis.
- Inflammation is also incited by acetaldehyde which, when bound covalently to cellular proteins, forms adducts that are antigenic.
- Earliest changes in alcoholic hepatitis are located predominantly around the central vein seen in histology.
- Alcohol is known to cause an exaggerated gradient of hypoxia from the portal vein to the central vein, suggesting that the hypoxia induced by chronic alcohol use may contribute to hepatic damage[5].
- Tanaka and co-workers showed in a recent study of over 1200 patients that coffee consumption protected males from the induction of γ-glutamyltransferase by alcohol and may possibly protect against liver cell damage caused by alcohol[7].

Histological Features of ALD

- Steatosis (fatty liver)
- Mallory's hyaline bodies
- Cholestasis
- Liver fibrosis
- Micronodular cirrhosis

CLINICAL FEATURES

Screening blood test may reveal significant liver disease due to alcohol without any clinical manifestation. Some patients may presents with nonspecific symptoms like nausea, vomiting, diarrhoea, abdominal

pain or discomfort. If the patient comes to clinic to seek help for detoxification, investigation reveals the degree and extent of damage caused by alcohol. ALD may be found when the patient comes for alcohol related problems of other organs, i.e. pancreas, heart, brain and peripheral nerves, etc.

Patients with *Fatty liver (Steatosis*) are usually well and asymptomatic or have nonspecific symptoms. Liver may be enlarged but non tender. Features of chronic liver disease are absent liver enzymes may be mildly raised.

Presentation of *Acute alcoholic hepatitis* vary considerably. The patient may look quite well with nonspecific symptoms or very ill, malnourished with specific features of hepatic insufficiency or encephalopathy. Physical signs include enlarged tender liver, jaundice, ascitis pyrexia, spider angioma or signs of encephalopathy. Blood results may show anemia, leukocytosis, high bilirubin and enzymes, prolonged prothombin time and low albumin. They are prone to have infections.

Alcoholic cirrhosis may present with features of decompensation or any other alcohol-related clinical problems. Patients may have jaundice, pruritus, low platelets and albumin, coagulopathy or complications of portal hypertension such as variceal bleeding, ascites, or hepatic encephalopathy[8]. Spider telangiectasia, parotid enlargement, gynecomastia, and hepatomegaly are more common in alcoholic cirrhosis.

Presenting Features of ALD

- Abdominal pain/discomfort
  Hepatomegaly
- Nausea/vomiting — Ascites
- Diarrhoea — GI bleeding
- Pyrexia — Encepalopathy
- Jaundice — Spider telangiectasia
- Parotid enlargement — Gynecomastia

DIAGNOSIS

The diagnosis is based on a thorough history, physical examination, and investigation results.

History

For a reliable account of prolonged alcohol abuse, it is important to gain the trust of the patient. Often the collateral history from spouse, family members, and friends is useful. For assessment, various question formats, i.e. CAGE test, are helpful.

CAGE questionnaire for assessing ALD patients

C. Have you ever felt the need to cut-down your drinking?

A. Have you ever felt annoyed by criticism of your drinking?

G. Have you ever felt guilty about your drinking?

E. Have you ever taken a drink (eye opener) first thing in the morning?

Score 1 for each positive response.

A score of 2 or more suggests alcohol excess.

Laboratory Tests

Significantly raised serum γ-*glutamyltransferase (γ- GT)* and *Mean Corpuscular Volume* (MCV) are most important and valuable for detection of alcohol excess. However, moderate rise of *γ-GT* may be found in nonalcoholic fatty liver drugs like phenetoin causing enzyme induction.

Liver function tests – Elevated *Serum transaminase* level **ALT and AST** are not specific. These are mildly raised in fatty liver. Characteristically, the AST:ALT ratio is about 2:1, and the absolute value of the ALT does not exceed 300 U/L unless a superimposed hepatic insult exists, such as paracetamol toxicity. If raised 5 times of normal reference range, other diagnoses such as viral or autoimmune hepatitis should be considered.

Hyperbilirubinemia reflects the severity of the hepatitis and is greatly increased in alcoholic hepatitis. Prolongation of the *prothrombin time and hypoalbuminemia* reflect poor hepatic synthetic function. A score based on prothrombin time (seconds) and serum bilirubin (mmol/L) is used to determine short term prognosis in alcoholic hepatitis.The discriminant function (DF) is calculated from the equation DF = 4.6 (prothrombin time-control time) + serum bilirubin/17.1. A score >32 denotes severe disease with a two months mortality of 50% and these patients should be given a trial of corticosteroids[9].

Procollagen III propeptide, laminin, and type IV collagen are serum makers of fibrosis indicate severity of liver injury. However, their sensitivity and specificity is not adequate for using in individual cases.

Full Blood Count

Anemia and Leukocytosis is common in alcoholic hepatitis. *Thrombocytopenia*, may occur due to direct alcohol toxicity or hypersplenism found in portal hypertension along with anemia and leucopenia.

Electrolytes

Hyponatremia and hypokalemia are quite common and seen less commonly are hypocalcemia and hypomagnesemia.

Liver Biopsy

Liver biopsy is not routinely necessary to diagnose liver injury. For fatty liver, biopsy is rarely required and may be useful in excluding steatohepatitis or fibrosis. An isolated raised **γ-GT** in a heavy drinker with otherwise normal liver function tests is usually associated with only mild histological liver damage, which is reversible.

Histological Findings

Fatty liver: Fat accumulation in liver cells, usually macrovesicular and rarely microvesicular commonly affecting centrilobular region. In severe fatty liver, however, fat is distributed throughout the acinus[10].

***Alcoholic hepatitis*:** Inflammation and necrosis occurs, most prominently in the centrilobular area of hepatic acinus. Ballooning of hepatocytes is classical. They compress sinusoids and lead to portal hypertension which is reversible. Inflammatory exudates contain polymorphonuclear cells and mononuclear cells. There may be fatty infiltration and Mallory bodies (intracellular perinuclear aggregations of intermediate filaments that are eosinophilic on hematoxylin and eosin staining). These are not specific for alcoholic hepatitis[9].

Alcoholic cirrhosis is diagnosed on finding the classic signs and symptoms of end-stage liver disease in a patient with a history of significant alcohol intake.

End-stage alcoholic cirrhosis (in the absence of acute alcoholic hepatitis) resembles with those of advanced liver disease from many other causes, without any distinct pathologic findings[8].

However, if the diagnosis is not certain, then only liver biopsy can be justified. It is also useful to rule out other unsuspected causes of liver disease, providing clear information of the extent of the damage, predicting prognosis, and helping to decide treatment mode[15].

Transjugular venous route is used to perform biopsy in patients of ALD with coagulopathy, where transcutaneous biopsy is not possible.

Ultrasound Scanning (USG)

This is a very useful screening method. Characteristic findings on USG include a hyperechoic liver with or without hepatomegaly.

It can reveal the presence of fatty liver and hepatitis through changes in the reflectivity of the liver parenchyma. In severe cirrhosis, the liver is shunken, irregular or nodular alongwith ascites, dilated portal vein varices and splenomegaly, suggesting portal hypertension.

Doppler studies can demonstrate changes in hepatic artery and portal vein flow. Newer radiological tools such as magnetic resonance spectroscopy are being evaluated[11].

Portal pressure measurements taken at hepatic venography may be superior to the Child-Pugh score in predicting mortality and bleeding risk in patients with alcoholic cirrhosis but no previous bleeding[12].

TREATMENT

An integrated approach is needed to deal for detoxification for patients with acute alcohol problem. On admission to the hospital, control of clinical symptoms due to acute intoxication must be controlled urgently after hospital admission.

Abstinence is the most important for successful management of ALD patients. If the patient volunteers for assistance then the outcome is likely to be favorable. For sustained abstinence referral to a drug and alcohol dependency team or support group, i.e. alcohol annonymous should be done. Admission to hospital may be required for evaluation by clinical assessment/investigation, initiate the management and treating complications.

Nutritional Support

Most patients of ALD have some degree of malnutrition which is multi-factorial, mainly due to poor intake and reduced intestinal assimilation and storage in liver. Protein-calorie deficiency may increase the toxicity of alcohol by influencing the nutritional status on the integrity of the immune system and the capacity to respond to infection.

Protein calorie malnutrition correlates directly with short term and long term mortality. At 1 year from diagnosis of ALD, patients with mild malnutrition have 14% mortality compared with 76% mortality in those with severe malnutrition[13]. The precise mechanisms by which malnutrition enhances liver damage and worsens mortality in patients with alcoholic liver disease are unknown.

Adequate nutritional supplement is of immense value for their management. Usually, enteral nutrition is preferred. Protein supplement should be provided with positive nitrogen balance. If the patient develops encephalopathy, protein intake is restricted. Branched-chain amino acids are useful as a supplement to maintain positive nitrogen balance. However, they are quite expensive.

Schenker and Halff found that nutritional support improves nutritional status and abnormal liver tests, but does not decrease early mortality in patients with acute alcoholic hepatitis. Cabré, et al reported that nutritional support was associated with an improvement in serum albumin and an important reduction in mortality in the group of patients treated. Recent study showed enteral nutrition is as effective as prednisolone. Early deaths were more frequent with total enteral nutrition, whereas late deaths were more frequent with corticosteroids. Combination treatment appears to have more beneficial effect for ALD patient

Corticosteroids

This mode of treatment is specific for alcoholic hepatitis has received a lot of interest because of its role to initiate and perpetuate liver damage through immune system. Randomized, controlled trials, with corticosteroids (40 mg prednisolone daily, 28 days) in severe acute alcoholic hepatitis, suggested a significant decrease in short-term (30-day) mortality, but only in those with more severe liver dysfunction, as manifested by hepatic encephalopathy or a markedly abnormal discriminant function[14]. Results from other randomized controlled trials have been contradictory. Practice guidelines are in favor of corticosteroid therapy in severe alcoholic hepatitis if the diagnosis is certain[15].

Pentoxifylline

It inhibits tumor necrosis factor (TNF) synthesis. TNF is found to be high in serum and liver tissue in ALD which contributes to the high mortality . A randomized, double-blind, controlled trial showed that, Pentoxifylline-treated patients had a significant decrease in mortality (24% vs 46%, $P = 0.037$). The survival advantage resulted primarily from a decrease in the development of hepatorenal syndrome in pentoxifylline-treated patients (50% vs 91.7%, $P = 0.009$)[16]. Although promising, these findings have yet to be validated by independent investigations.

Metadoxine

Direct effect of metadoxine on alcohol metabolism promotes conversation of alcohol into acetaldehyde and subsequently its urinary excretion.

It prevents liver damage resulting from prolonged alcohol intake and helps in reversal of fatty liver degeneration. Hence,it is indicated for acute and chronic alcohol intoxication and fatty liver. IV bolus dose of 300 mg administered with or without standard treatment is quite well tolerated without any side effects. The same dose may be repeated if needed[15].

Propylthiouracil

It reduces the metabolism and oxygen consumption and has been used to reverse the hypermetabolic state of ALD. However, several randomized controlled trials do not show any significant effect on mortality, enzymes, histology or complications. Therefore, this treatment is not recommended for routine use[16].

Infliximab

After acute alcohol intake, TNF-α (a proinflammatory cytokine) causes inflammation and damage to liver cells. Infliximab neutralizes the effects by binding with TNF-α. However, several studies alone and with corticosteroids have not shown any distinct benefit and in a randomized study showed increased possibility of severe infection and short term death[17]. Therefore, its routine use is not recommended at present.

Naltrexone is an opiate antagonist and used in USA for over a decade has been licensed in the USA for patients who are actively drinking. It reduces craving and the level of drinking over several months but does not help in enhancing abstinence. *Nalmefene*, is new opiate antagonist. It is not hepatotoxic but data are insufficient at present to recommend its clinical use. *Acamprosate* reduces drinking frequency but its effect on abstinence is not clear. The mode of action of acamprosate is unknown but it appears to interact with glutamate receptors and calcium channels.

A recent meta-analysis has confirmed the clinical benefits of naltrexone and acamprosate. *Disulfiram* which has been traditionally used to promote abstinence, but recent studies do not recommend its use[18].

High dose vitamin B supplementation (oral or parenteral) can be used to combat vitamin B deficiency in ALD and also Wernicke's encephalopathy. Folate deficiency also occurs and should be given.

Chlormethiazole or chlordiazepoxide often used in reducing dosage to prevent withdrawal symptoms. Chlormethiazole intravenously is occasionally used in very agitated patients, but should only be used where close cardiorespiratory monitoring is available.

Silymarin is a natural antioxidant. It prevents liver damage caused by free radicals and hepatic lipid peroxidation. It increases glutathione synthesis inside the liver cell, stimulates protein synthesis and helps in the production of new liver cells to replace the damaged old ones. *L-ornithine, L-aspartate* enhances the production of energy in the liver cells by stimulating krebs cycle. It promotes ammonia detoxification and reduces ammonia level in the blood. In acute liver failure patients, it is usually given with IV infusion (6-8 amples/day), in chronic disease in the tablet or sachet form[19].

Following have been found useful in various studies but not used commonly: *Malotilate* has been used in the treatment of ALD because it inhibits CYP2E1 induced by alcohol. *S-adenosyl-L-methionine* dietary supplement therapy has been used in ALD as it replenishes liver mitochondrial glutathione levels. *Polyunsaturated fatty acids* potentiate alcohol induced liver injury by inducing cytochrome *P*-450 2E1. Fatty acid saturation decreases CYP2E1 activity and lipid peroxidation in rat studies. Long term *oxandrolone* has been used because of its anabolic effects (improved nitrogen balance) and its ability to accelerate the reversal of the fatty liver of ALD. It has shown benefit only in moderate disease. *Soya bean lecithin* is also a possibility because it can restore phosphatidyl choline levels and inhibit fibrosis mainly demonstrated in animal studies. *Thalidomide* has been considered in alcoholic hepatitis because it has anti-TNF properties. Glycyrrhizin acid based compounds **SNMCs** (Stonger Neo Minophagen-C) has been found very useful in acute and chronic disease

Other therapies that have been investigated in the treatment of alcoholic hepatitis, but not found to be beneficial include *insulin and glucagon, calcium channel blockers, and antioxidants such as vitamin E.*

LIVER TRANSPLANTATION

Indication for consideration of transplantation in a patient of ALD: Hepatic decompensation, features of chronic liver failure, i.e. encephalopathy, frequent ascitis, variceal bleeding, spontaneous bacterial peritonitis, elevated bilirubin, enzymes and prolonged prothrombin time, low albumin, etc. Most centers follow a six month abstinence rule before considering transplantation[20,21]. Many candidates are deemed unsuitable because of associated socioeconomic and psychiatric problems, coexistent alcoholic damage to other organs such as cardiomyopathy. A recent study from Birmingham noted a significant recidivism rate with patients often returning to alcohol intake in the first year after transplant[22]. These patients rapidly developed histological liver injury including fibrosis.

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