Alcohol and the liver

Ewan Forrest

Abstract

Hospital admission with alcoholic liver disease (ALD) has become increasingly common. Although there is a clear relationship between the risk of ALD and the dose of alcohol consumed, additional risk factors include genetic predisposition, gender, nutritional status, obesity, and co-existing liver diseases such as hepatitis C. ALD ranges from steatosis to alcoholic steatohepatitis and established cirrhosis. Several mechanisms are involved in the pathophysiology of ALD, including oxidative damage secondary to alcohol metabolism, and endotoxaemia leading to tumour necrosis factor α-mediated cell damage and death. Diagnosis requires a combination of a history of alcohol excess, clinical evidence of liver disease and compatible laboratory investigations, and the exclusion of other liver diseases. Liver biopsy may be necessary in cases of uncertainty. Presentation varies from incidental blood test abnormalities through to overt liver failure. The key to management is long-term abstinence and care should be delivered in conjunction with addiction services. Protein–calorie malnutrition is common and should be addressed along with specific thiamine replacement. Acute severe alcoholic hepatitis has a high mortality, and prognostic scores, such as the discriminant function and the Glasgow alcoholic hepatitis score, have been derived to identify those at highest risk and those who may derive short-term benefit from treatment with corticosteroids. Cirrhotic patients require hepatoma screening and variceal screening endoscopy. Liver transplant should be considered if the clinical condition does not improve despite a period of abstinence.

Keywords Alcohol; alcoholic hepatitis; alcoholic liver disease; cirrhosis

Epidemiology

In the UK, liver disease is the fifth most common cause of death and this death rate is increasing in contrast to that in many other Western European countries.[1] The major cause of these deaths is alcoholic liver disease (ALD). The average age of death from liver disease is just 59 years, compared with 82–85 years for those dying from cerebrovascular, heart or lung disease. There has been a fivefold increase in cirrhosis among people aged 35–55 years in the last 10 years.[2]

The population mortality from alcoholic liver disease is proportional to per capita alcohol consumption, and this has been shown to correlate closely with alcohol affordability. The current estimated cost of a hospital admission for a single episode of decompensated ALD is approximately £3400.[2] In 2012 in England, one in every eight hospital admissions for ALD resulted in death.[3]

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Risk factors

In addition to the clear relationship to the amount of alcohol consumed, other factors influence the development of ALD. Women are more susceptible to the hepatotoxic effects of alcohol and develop ALD more quickly than men who consume an equivalent daily amount of alcohol.[4] The most significant diet-related risk factor is obesity, with several studies showing that obesity is the single most important risk factor determining the risk of cirrhosis in heavy drinkers.[5] Twin studies have indicated the importance of genetic susceptibility to ALD, showing that monozygotic twins have a higher prevalence of alcohol-related cirrhosis than dizygotic twins.[6] Such studies suggest that genetic factors may represent up to 50% of an individual's susceptibility to ALD, although the search for specific polymorphisms has so far been unsuccessful.[7] Co-existent hepatitis C infection increases the risk of cirrhosis 30-fold in those who take alcohol to excess.[8]

Pathophysiology

The pathophysiology of ALD is complex with multiple mechanisms of possible hepatocyte damage. Metabolism of alcohol to acetaldehyde and then to acetate by their respective dehydrogenases leads to the production of reduced nicotinamide adenine dinucleotide (NADH), which inhibits fatty acid oxidation and promotes fat accumulation. Alternative metabolism of alcohol by the cytochrome P450 enzyme 2E1 leads to the production of reactive oxygen species, causing lipid peroxidation and inflammation.

Alcohol also increases intestinal permeability, leading to endotoxaemia. This causes Kupffer cells in the liver to release tumour necrosis factor α (TNFα), which in turn leads to more oxidative stress. In addition, acetaldehyde may form protein adducts that can act as neo-antigens, triggering immune-mediated damage (Figures 1 and 2). The results of these multiple 'hits' on the liver leads to hepatocyte necrosis, but perhaps more significantly apoptosis.

Pathology

The term ALD encompasses alcoholic steatosis, with or without significant fibrosis (in up to 100% of drinkers with a daily alcohol intake of greater than 60 g/day), alcoholic steatohepatitis (in 10–35%), and established cirrhosis (in approximately 15%).[9] The natural history of ALD appears to progress liver through steatosis to fibrosis and cirrhosis with some, but probably not all, patients also passing through a phase of alcoholic hepatitis. The steatosis is macrovesicular and predominantly in perivenular hepatocytes. The features of alcoholic hepatitis are a perivenular steatohepatitis, often with Mallory bodies, hepatocyte ballooning, megamitochondria, canalicular cholestasis and a neutrophil infiltrate. With repeated episodes of injury, regenerative nodules and perivenular fibrosis develop leading to micronodular cirrhosis.

Diagnosis

The history should document the type and pattern and amount of alcohol consumed. Screening tools for harmful alcohol use include the AUDIT questionnaire or its abbreviated forms, the

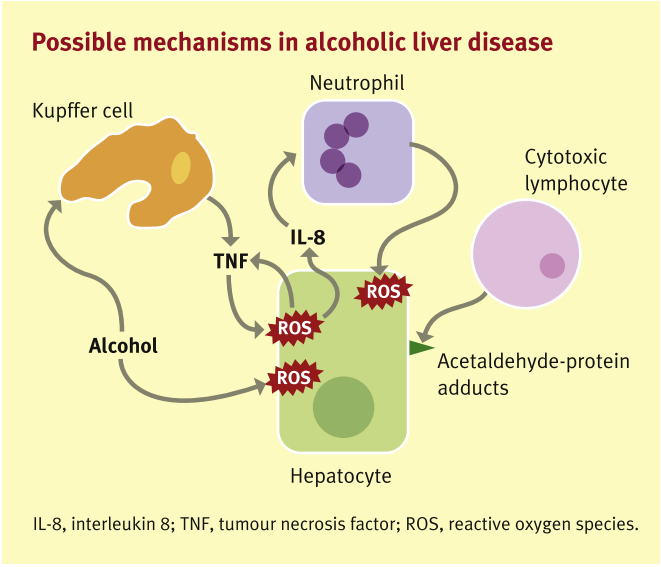

Figure 1

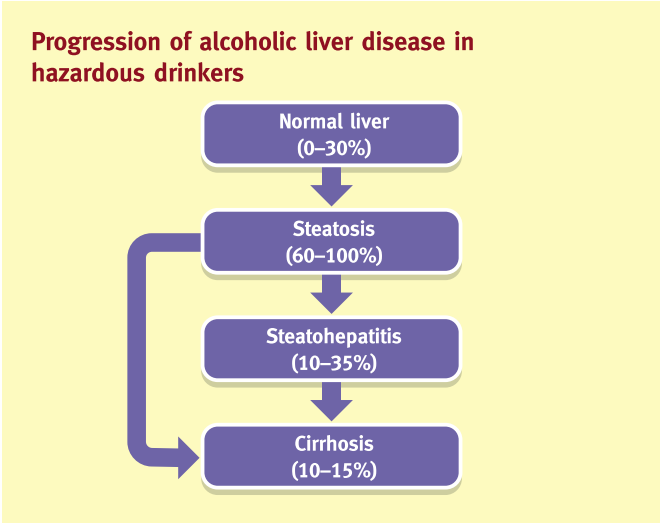

Figure 2

FAST and AUDIT-C.[10] However, it is important to know that not all patients with ALD have alcohol dependency.

A diagnosis of ALD can be made in most patients with a combination of a history of alcohol excess, clinical evidence of liver disease and compatible laboratory investigations. However, as only the minority of alcohol misusers develops significant ALD, other forms of liver disease should be excluded. A screen for chronic viral, autoimmune and hereditary liver disease should be carried out. Up to 20% of people with alcoholic liver disease will have another co-existent liver disease such as viral hepatitis. An ultrasound scan (USS) of the abdomen should be performed to identify obstructive, structural or neoplastic disease, with Doppler of the portal and hepatic veins. Further imaging can be undertaken with either computed tomography or magnetic resonance imaging if other pathology is suspected.

In cases of doubt, a liver biopsy can be a useful tool to exclude other causes of liver disease. However, percutaneous liver biopsy may be contra-indicated in the clinical setting by the presence of ascites and/or a coagulopathy. Risks can be minimized by performing liver biopsy via the transjugular route.

Presentation

Presentation varies from an incidental discovery of abnormal liver blood tests to acute-on-chronic liver failure or decompensated cirrhosis. In ALD, serum aspartate aminotransferase (AST) is rarely more than 500 IU/litre, serum alanine aminotransferase (ALT) rarely over 300 IU/litre and the AST:ALT ratio usually more than 1.5. Patients presenting only with abnormal liver blood tests may have simple steatosis, but may have 'silent' cirrhosis. Clues to the presence of chronic liver disease, such as stigmata of chronic liver disease (spider naevi, palmar erythema, gynaecomastia) or portal hypertension (caput medusae, otherwise unexplained thrombocytopenia) should be sought.

Acute alcoholic hepatitis is characterized by the new onset of jaundice (serum bilirubin >80 μmol/L), often associated with other features such as pyrexia, a peripheral leucocytosis, hepatomegaly, or a hepatic bruit. There may be other features of decompensated liver disease such as encephalopathy and ascites. The majority of patients with alcoholic hepatitis will have co-existent cirrhosis.

Patients may present with decompensated chronic liver disease in a more insidious fashion. They may have peripheral oedema, ascites and encephalopathy but are not necessarily jaundiced. Evidence for precipitants of hepatic decompensation, such as sepsis, gastrointestinal bleeding, electrolyte imbalance or the development of hepatocellular carcinoma, should be sought.

Treatment

Abstinence

The cornerstone to the management of ALD is long-term abstinence. Brief interventions (5–20-minute consultations) carried out opportunistically in the hospital setting can have an effect for up to 1 year.[10] Alcohol dependency should ideally be managed in concert with addiction services to ensure appropriate intervention and community follow-up. Patients admitted acutely with ALD are at risk of alcohol withdrawal syndrome. Oxidative metabolism of benzodiazepines may be impaired in those with advanced disease and shorter-acting agents that undergo primary glucuronidation, such as lorazepam, should be considered.

Nutrition

Patients with alcoholic liver disease are typically in a hypercatabolic state with protein–energy malnutrition. This is of prognostic significance and increases the likelihood of complications such as infection, encephalopathy and ascites. Protein and calorie nutritional support should be provided, either as dietary supplements or via enteral feeding regimens, aiming for a daily intake of protein up to 1.2–1.5 g/kg and of calories up to 35–40 kcal/kg. Thiamine replacement should be prescribed to prevent the development of Wernicke's encephalopathy, in accordance with published guidelines.[9] Studies have not shown that specific anti-oxidant treatment is beneficial in alcoholic hepatitis.