Alcohol Liver Disease: Review

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Summary

More, than last anniversary occurs dramatically increase hospital admission of patients with alcoholic liver disease (ALD). 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 a-mediated cell damage and death. Diagnosis requires a combination of a history of alcohol excess, clinical evidence of liver dis- ease 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 longterm abstinence and care should be delivered in conjunction with addiction services. Proteinecalorie malnutrition is common and should be addressed along with specific thiamine replacement. Acute severe alco- holic 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.

Key words: *Alcohol, alcoholic hepatitis, alcoholic liver disease, cirrhosis.*

Epidemiology

In most of European countries, 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.

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] Coexistent 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 a (TNFa), which in turn leads to more oxidative stress.

In addition, acetaldehyde may form protein adducts that can act as neoantigens, triggering immunemediated damage . 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 10e35%), and established cirrhosis (in approximately 15%).

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 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 dis- ease, 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 amino- transferase (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 mmol/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 absti- nence. Brief interventions (5e20-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 proteineenergy malnutrition. This is of prognostic significance and increases the likelihood of compli- cations 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 1.2e1.5 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.

Acute alcoholic hepatitis

Severe acute alcoholic hepatitis has a 28-day mortality of up to 60%. A clinical diagnosis of alcoholic hepatitis still encompasses a wide spectrum of disease. Assessment of the severity of alcoholic hepatitis is vital not only to identify those patients with a poor prognosis, but also to target treatment effectively. The discriminant function (DF) has been used for this purpose; a value more than 32 is associated with a poor prognosis.[11] However, the DF suffers from a lack of specificity and overall accuracy, and relies upon the measurement of prothrombin time, which can vary significantly between different laboratories. The Glasgow alcoholic hepatitis score (GAHS) is a more accurate score that has been validated throughout the UK. A value of 9 or more is associated with a poor prognosis.[12] Both the DF and the GAHS have been used to identify patients who will benefit from specific treatment. The model for end-stage liver disease (MELD) score has been used to assess prognosis in alcoholic hepatitis, but the threshold for identifying poor outcome remains unclear and the MELD score has yet to be shown to identify patients likely to benefit from additional treatment.

Use of corticosteroids in alcoholic hepatitis has been controversial. The STOPAH trial, the largest study of alcoholic hepatitis ever performed, has addressed this question.[13] Over 1000 pa- tients with a DF greater than 32 were randomized to corticosteroids or pentoxifylline in a factorial design. Overall mortality was not significantly different between the four groups, but multi- variate logistic regression showed that corticosteroid use was associated with an improved 28-day survival, although this benefit was lost by 90 days.[13] Serious infections were more likely in corticosteroid-treated patients. Pentoxifylline was not seen to be beneficial on analysis at any time point despite a previous study suggesting benefit.[14] Other studies have confirmed that pentoxifylline added to corticosteroids offers no advantage.[15] The addition of acetylcysteine to corticosteroids may be of benefit by reducing sepsis episodes, but confirmatory studies are required before this can be recommended routinely.[16]

Overall, benefit with corticosteroids in this patient group would appear to be short-lived. However, this may relate to the poor specificity of the DF in identifying those who might benefit, whereas the GAHS may be a better guide. In a retrospective study, patients with a GAHS less than 9 did not appear to benefit from corticosteroid treatment, whereas those with a GAHS of 9 or more showed improved 28 and 84-day survival.[17] Further analysis of the STOPAH data with regard to the performance of alternative prognostic scores is awaited and may shed light on this area.

A fall in serum bilirubin after a week of corticosteroid treat- ment is associated with a survival benefit. From this observation the Lille score has been developed to identify complete, partial and non-responders to corticosteroid treatment.[18] However, a simpler index of response e a 25% reduction in serum bilirubin from baseline after approximately 1 week of treatment e may be equally able to identify such 'responders' to treatment.[19]

The clinical presentation of alcoholic hepatitis can mimic sepsis. Patients should be screened for infection with a chest X- ray and culture of urine, blood and ascitic fluid as appropriate.

Cirrhosis

The complications of alcohol-related cirrhosis, such as ascites, variceal haemorrhage and encephalopathy, should be managed in the same way as for other forms of chronic liver disease. Patients with cirrhosis should have 6-monthly USS and aFP for hepatocellular carcinoma screening, and screening endoscopy for oesophageal varices. Long-term prognosis is closely related to the stage of disease, as assessed by standard chronic liver disease scores such as the MELD score or the ChildePugh score. Clearly, the prognosis is improved by sustained abstinence.

Liver transplantation

Liver transplant should be considered for those patients whose clinical condition remains poor despite sustained abstinence. Although there is no requirement for a set period of abstinence before considering liver transplant, many patients will improve clinically for up to 6 months after stopping drinking. This improvement might render referral for transplant unnecessary. Those patients who are assessed for transplant require a rigorous psychiatric evaluation. Liver transplant for alcoholic hepatitis has been suggested for those who do not respond to corticoste- roids ('Lille non-responders'),[20] but concerns remain about the suitability of such intervention and whether the Lille score is specific enough to identify those with little chance of survival.[21]

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