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Alcoholic steatohepatitis

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Severe alcoholic steatohepatitis has a poor prognosis and is characterized by jaundice and signs of liver failure. Its incidence is unknown, but prevalence is around 20% in cohorts of alcoholics undergoing liver biopsy. Diagnosis is established with elevated liver transaminases, neutrophil counts, serum bilirubin, and impaired coagulation and a history of excessive alcohol consumption, and exclusion of other etiologies. Histology is helpful but not mandatory. Prognostic scores include the Maddrey's discriminant function, the model of end-stage liver disease, and the Glasgow Alcoholic Hepatitis Score. Pathophysiology involves hepatic fat storage, increased hepatic uptake of gut-derived endotoxins triggering Kupffer cell activation and release of proinflammatory triggers, induction of cytochrome P4502E1 producing toxic acetaldehyde and reactive oxygen species, and ethanol-mediated hyperhomocysteinemia causing endoplasmic reticulum stress. Treatment includes abstinence, enteral nutrition, corticosteroids, and possibly pentoxifylline. A debate is ongoing whether certain patients with severe alcoholic steatohepatitis could be eligible for liver transplantation.

Introduction

Alcohol consumption is high in Europe, Russia and North America and its abuse a major cause of preventable morbidity and mortality in many countries [1]. The burden of disease is high and alcoholism is responsible for 3.8% of global deaths and 4.6% of disability-adjusted life years [2], mainly due

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to causing alcohol dependence, neuropsychiatric disorders, chronic pancreatitis, certain cancers [3] and – most frequently – alcoholic liver disease (ALD). The latter encompasses alcoholic steatosis with or without significant fibrosis in up to 100% of drinkers with a daily alcohol intake of >60 g/day, and established cirrhosis in approximately 15% of patients. Although often grouped into these three distinct stages, ALD subtypes often overlap in an individual. Alcoholic steatohepatitis (ASH) is characterized by typical clinical, laboratory and histomorphological features and evolves in chronic alcohol abusers after several years of excessive drinking, and even after alcohol consumption has been significantly reduced or stopped. Patients are predominantly male although women drinking equal amounts are at higher risk for ASH. There is – like with alcoholic cirrhosis – a dose-relationship between the amount of alcohol and the likelihood of ASH which is highest above 120 g/day [4,5]. While the true incidence of ASH is unclear, its prevalence is around 20% among subjects who undergo liver biopsy [6], and is suspected in 10–35% of hospitalized alcoholics [7]. Less severe forms of ASH frequently respond to alcohol abstinence, whereas the prognosis of severe ASH is poor. Up to 40% die within 6 months upon onset of symptoms due to liver failure, severe infections including spontaneous bacterial peritonitis, portal hypertension with variceal bleeding, and hepatorenal syndrome [8].

Clinical presentation and diagnosis of ASH

Severe ASH should be considered if regular alcohol consumers present with rapid onset of jaundice and clinical and biochemical signs of impaired liver function. Some patients develop fever and on physical examination the liver is usually tender and enlarged. Parotid hypertrophy and Dupuytren's contracture are typical but not specific for ALD, let alone ASH [9,10]. The may be more specific if accompanied by other manifestations of chronic alcohol toxicity, i.e. polyneuropathy, cardiomyopathy and a history of chronic pancreatitis [11,12]. A typical finding in patients with ASH is a wasting syndrome due to severe malnutrition reflected by muscle atrophy, low serum albumin levels, a negative nitrogen balance and hypovitaminosis of B vitamins, retinoids, vitamins C, E and zinc [13,14]. Some patients with severe hypovitaminosis A even report night blindness due to depletion of retinol [15]. Regarding routine laboratory, serum aminotransferase levels are usually raised 5–8-fold (rarely more than 300 U/l), characteristically with a preponderance of aspartate aminotransferase (AST) to alanine aminotransferase (ALT). With this, the ratio of AST to ALT increase is typically >2 and, thus, distinct from viral or drug-induced hepatitis in which ALT elevation is usually more prominent [16]. This enzyme elevation pattern relates to an alcohol-related deficiency of pyridoxal 5′-phosphate and significant alcohol-induced damage of mitochondria which, upon alcohol-mediated injury, release AST [13,17]. Elevation of neutrophilic granulocytes may be a direct indicator of ASH unrelated to infectious triggers. However, bacterial infections are frequent among patients with ASH, and should be sought as patients often suffer from pneumonia, urinary tract infection, spontaneous bacterial peritonitis and dental infections [18]. Thrombocytopenia is frequent and related either to alcohol directly or/and to splenomegaly due to portal hypertension. Often, patients with ASH reveal increased international normalized ratio (INR) values and prolongation of prothrombin time indicating impaired liver function. Along with this, alterations of kidney function with elevation of serum creatinine may be present indicating imminent hepatorenal syndrome. A liver biopsy can be helpful to confirm the diagnosis of ASH and is recommended in the newly released practice guidelines issued by the American Association for the Study of Liver Disease (AASLD), however, it is not mandatory [19]. Biopsies can be performed either percutaneously or via the transjugular route, the latter particularly in patients with impaired coagulation, ascites or in whom information about the severity of portal hypertension is wishful. Histology in ASH is characterized by neutrophilic infiltrates which often surround eosinophilic inclusion bodies termed Mallory-Denk bodies. Most patients with ASH have significant steatosis of more than 30% of hepatocytes, and reveal perivenular fibrosis as opposed to periportal fibrosis in chronic viral hepatitis [20]. In addition, significant hepatocellular ballooning and a 'chicken wire'-like pattern of fibrillar collagen deposition are regularly found (Fig. 1).

Imaging techniques are part of the work-up of patients with suspected ASH, however, neither ultrasound nor computed or magnetic resonance tomography is diagnostic. Transient elastography can assist the assessment of liver fibrosis in ALD [21], but is markedly confounded by elevated liver enzyme levels and cholestasis [21,22].