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Alcoholic hepatitis: Prognosis and treatment

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Abstract Alcoholic hepatitis (AH) is a type of acute-on-chronic liver failure and is the most severe form of alcoholic liver disease. AH occurs in patients with heavy alcohol abuse and underlying liver disease. In its severe form, AH carries a poor short-term prognosis. Although the existence of AH can be strongly suspected based on clinical and biochemical criteria, a definitive diagnosis requires a liver biopsy. There is a clear need to develop non-invasive markers for these patients. The prognosis of patients with AH can be established by different score systems (Maddrey's DF, ABIC, MELD and Glasgow). Recently, a histological scoring system able to estimate prognosis has been developed (Alcoholic Hepatitis Histological Score – AHHS). The management of patients with AH has changed little in the last few decades. In patients with severe form of AH, prednisolone and pentoxifylline are the first line therapy. Unfortunately, many patients do not respond and novel targeted therapies are urgently needed. Current research is aimed at identifying the main disease drivers and to develop animal models of true AH. For non-responders to medical therapy, the only curative option is to perform a salvage liver transplantation. This particular indication of liver transplantation is currently under debate and prospective studies should evaluate the specific patient evaluation and selection criteria.

PALABRAS CLAVE
Hepatopatía alcohólica;
Guía clínica;
Trasplante hepático

Hepatitis alcohólica: pronóstico y tratamiento

Resumen La hepatitis alcohólica (HA) es un tipo de fallo hepático agudo sobre crónico y es la manifestación más severa de la hepatopatía alcohólica. La HA ocurre en pacientes con ingesta muy elevada de alcohol y con hepatopatía de base. En sus formas severas, la HA conlleva un pésimo pronóstico. La existencia de una HA puede ser sospechada combinando criterios clínicos y analíticos. Sin embargo, el diagnóstico definitivo de una HA requiere una biopsia hepática. El pronóstico de los pacientes con HA puede realizarse mediante diferentes escalas (Maddrey's DF, ABIC, MELD y Glasgow). Recientemente, se ha descrito una escala histológica capaz de estimar el pronóstico de estos pacientes (Alcoholic Hepatitis Histological Score -AHHS-). El manejo de los pacientes con HA no ha cambiado en exceso en las últimas décadas. Para los pacientes con

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formas severas, los tratamientos de primera línea son la prednisolona y la pentoxifilina. Desgraciadamente, muchos pacientes no responden y nuevas terapias moleculares son necesarias. En la actualidad, la investigación se centra en la identificación de los responsables moleculares de esta enfermedad y en el desarrollo de modelos animales de HA. Para los pacientes que no responden a la terapia médica, la única opción curativa es realizar un trasplante hepático. Esta indicación de trasplante está en debate en la actualidad y estudios prospectivos deberían determinar los criterios de evaluación y de selección de estos pacientes.

Introduction

Alcoholic liver disease (ALD) is one of the commonest causes of advanced liver disease worldwide. The disease spectrum ranges from fatty liver to steatohepatitis, progressive fibrosis and hepatocellular carcinoma[1] (Fig. 1). ALD is one of the leading factors of liver fibrosis in the general population as well as cirrhosis.[2] Compared to the recent advances in viral hepatitis, few advances have been made in its prevention, early diagnosis and treatment of ALD. The lack of advances in the field of ALD are due to intrinsic difficulties in performing clinical trials in patients with an active addiction, a poor knowledge of molecular drivers in humans and the lack of experimental model of advanced ALD.

Patients with chronic alcohol misuse can present with histological criteria of steatohepatitis (ASH) at different stages of the disease.[3] This early form is poorly characterized in humans and there is a clear need to delineate its natural history and prognostic factors as well as to develop reliable non-invasive markers. Early detection of initial forms of ALD in the primary care setting and subsequent behavioral interventions should be encouraged. Although the lesions defining ASH do not differ from those described in non-alcoholic steatohepatitis (NASH), ASH is usually associated with more severe histological lesions and a worse clinical course. In addition, patients with advanced ALD (in most cases cirrhosis) and active drinking can develop an episode of acute-on-chronic liver failure named ''alcoholic hepatitis'' (AH).[1] In most alcoholic patients with this clinical syndrome, the histological analysis shows the presence of ASH and advanced fibrosis. In its severe forms, AH carries a bad prognosis and current therapies are not fully effective. This article summarizes the clinical, analytical and histological features of AH and discusses the therapeutic options for these patients.

Clinical presentation

AH should be considered as a clinical syndrome defined by the recent onset of jaundice and/or liver decompensation (i.e. ascites) in a patient with chronic alcohol abuse. In the past, AH was referred to as ''acute alcoholic hepatitis'', however the term ''acute'' is not entirely accurate. Although the clinical presentation may present abruptly, it is felt to reflect an exacerbation of underlying chronic liver disease. It is important to clarify that while AH is a clinical syndrome, the existence of ASH needs to be confirmed histologically.

The hallmark of symptomatic AH is the abrupt onset and/or rapid progression of jaundice, which may or may not be associated with fever, infection, weight loss, malnutrition, and an enlarged, tender liver. In severe cases, AH may induce liver decompensation with ascites, encephalopathy, or gastrointestinal bleeding. Laboratory evaluation typically demonstrates AST levels that are elevated to 2–6 times the upper limit of normal with an AST/ALT ratio that is greater than 2. Increased bilirubin and neutrophilia are also frequently observed. Serum albumin may be decreased, prothrombin time prolonged and the international normalized ratio (INR) may be elevated; however, these values depend on the severity of the episode. Patients with severe AH are prone to develop bacterial infection and acute renal failure due to type 1 hepatorenal syndrome.[4]

Although the existence of AH can be highly suspected based on clinical and analytical criteria, a definitive diagnosis requires histological confirmation. Due to the existence of coagulopathy in most patients, a transjugular biopsy is frequently indicated in this setting. In most cases, advanced liver fibrosis (mainly cirrhosis) and superimposed ASH are found. When using a Tru-Cut instead of a fine needle, most patients show signs of cirrhosis. ASH is defined by the coexistence of steatosis, hepatocyte ballooning and/or Mallory-Denk bodies, and an inflammatory infiltrate with PMNs. A typical finding in many patients is the presence of megamitochrondria. Importantly, canalicular and/or lobular bilirubinostasis is commonly seen in AH, especially in patients with ongoing bacterial infections. It is important to note than in 20–25% of patients, a true ASH is not found. Other histological findings include signs of drug-induced liver disease, ischemic hepatitis (especially in patients with cocaine consumption), foamy hepatic degeneration and biliary obstruction.

The incidence of AH remains largely unknown. A Danish population-based retrospective cohort study estimated that it ranges from 24 to 46 per million, depending on gender, and is increasing.[5] A large study, where systematic liver biopsies were performed in 1604 alcoholic patients, found the prevalence of AH to be approximately 20%.[6] In symptomatic patients, including those with decompensated liver disease, the prevalence of AH is not well known, partly because most centers rely on clinical criteria rather than transjugular liver biopsy as routine practice in the diagnosis of patients with decompensated ALD. Relying only clinical criteria alone carries a 10–50% risk of misclassifying patients as having or not having AH.[7–9] Therefore, the recently published EASL Practical Guidelines on Alcoholic Liver Disease[10]