Grand Rounds

JOURNAL OF HEPATOLOGY

Grand Rounds: Alcoholic Hepatitis

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Keywords: Alcoholic liver disease; Liver biopsy; Corticosteroids; Liver transplantation.

Received 24 January 2018; received in revised form 20 April 2018; accepted 1 May 2018

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Clinical vignette

A 33-year-old Caucasian male was admitted to hospital with recent onset of jaundice of 2–3 weeks duration. He reported heavy use of alcohol for the last 10 years with the last drink a day prior to the onset of symptoms. At admission, he was alert and oriented to time, place, and person, and was deeply jaundiced. His laboratory profile can be summarised as follows: haemoglobin 12.1 g/dl, white blood cell count 18,700 with 81% neutrophils, serum bilirubin 33 (direct 22) mg/dl, aspartate aminotransferase 147 IU/L, alanine aminotransferase 62 IU/L, alkaline phosphatase 117 IU/L, serum albumin 2.8 gm/dl, serum creatinine 0.6 mg/dl, prothrombin time 18.3 (control 14.5) seconds, and international normalized ratio 1.48. He was diagnosed with severe alcoholic hepatitis (Maddrey discriminant function score of 50) and treated with prednisolone for 28 days with symptomatic and biochemical improvement. His Lille score at seven days was 0.4, and his serum bilirubin had decreased to 3.5 mg/dl at the end of treatment. He was also seen by the addiction team during hospitalisation; he agreed to follow through on recommendations. He was dismissed after completing a three-week inpatient rehabilitation programme but relapsed to alcohol use three months later, and was readmitted with alcohol withdrawal. He was readmitted two months later (about six months from the first episode) for a second episode of severe alcoholic hepatitis. At admission, his model for end-stage liver disease score was 32 and he was treated again with corticosteroids. His Lille score at seven days was 0.6 and steroids were discontinued. The hospital course was complicated by spontaneous bacterial peritonitis and pneumonia with development of acute kidney injury. He continued to worsen, developing multiorgan failure. After a course of one month, the family's preference was for him to receive comfort measures.

This scenario raises several questions:

I. Should liver biopsy have been carried out in this patient before starting treatment for alcoholic hepatitis?
II. What should the protocol be for early diagnosis of infection?
III. Are there options other than steroid therapy for severe alcoholic hepatitis? Should pharmacological therapy have been initiated to prevent alcohol relapse?
IV. What are the determinants of short-term and long-term prognosis in alcoholic hepatitis?
V. What is the role of liver transplantation in alcoholic hepatitis?

Introduction

Alcoholic hepatitis (AH) is a clinical syndrome occurring in patients with chronic and active heavy alcohol use. Patients present with jaundice and systemic inflammatory response syndrome (SIRS) and may progress to acute-on-chronic liver failure. Patients with severe AH have mortality of up to 30–40% at 28 days from the initial presentation. Optimal management requires a team including a hepatologist, addiction specialist, nutrition expert and a social worker. Corticosteroids are the only available medical therapy for specific treatment of patients with severe AH. However, use of corticosteroids is limited by non-response in approximately 40% of patients, potential for side effects, and lack of mortality benefit beyond one month. Over the last few years, there has been an increasing interest in early liver transplantation as salvage therapy for non-responders to corticosteroids. However, despite consistent reports of benefit, barriers remain to universal acceptance of early liver transplantation.

I. Should liver biopsy have been carried out in this patient before starting treatment for alcoholic hepatitis?

To answer this question, we will discuss clinical criteria for diagnosis of AH before discussing the role of liver biopsy.

Clinical criteria for diagnosis of alcoholic hepatitis

Alcoholic hepatitis should be suspected in patients with known alcoholic liver disease or heavy alcohol use for >6 months who present with recent onset or worsening of jaundice with <60 days of abstinence before the onset of jaundice. Clinical diagnosis of AH requires demonstration of heavy alcohol use as the aetiological factor in the

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Please cite this article in press as: Singal AK et al. Grand Rounds: Alcoholic Hepatitis. J Hepatol (2018), https://doi.org/10.1016/j.jhep.2018.05.001

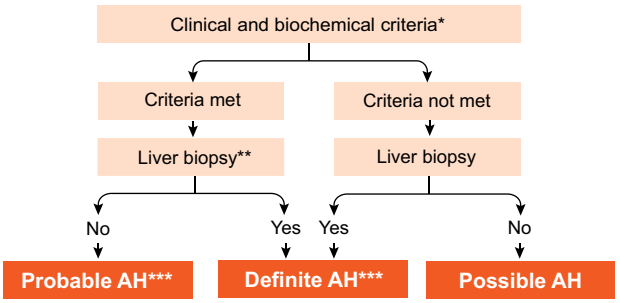

Fig. 1. Algorithm for diagnosis of alcoholic hepatitis. *Clinical criteria: Heavy alcohol use (>2 drinks in females and >3 drinks in males) for >5 years; Active alcohol use until at least 8 weeks prior to presentation; Recent (<1 month) onset or worsening of jaundice; Exclude other liver diseases, biliary obstruction, HCC. *Biochemical criteria: Serum bilirubin >3 mg/dl, AST >50 and <500, AST >ALT by 1.5:1; **Transjugular route preferred for obtaining the liver tissue. **Characteristic histological findings: Cell balooning, neutrophil infiltration, cholestasis, varying degree of steatosis and fibrosis. ***Needed for inclusion in clinical trials and before starting specific pharmacologic therapy. AH, alcoholic hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma.

absence of other known causes of liver disease, and the presence of hepatitis. The threshold for the absolute amount of alcohol consumed, that is, the amount and duration of alcohol use, is unknown. Average consumption of three or more drinks (40 grams) per day for women and four or more drinks (50–60 grams) per day for men is accepted as a minimal threshold for diagnosis of AH. Alcohol use is typically for years, and for diagnosis of AH should include the period within two months of presentation. Hepatitis requires a clinical diagnosis, with manifestations including rapid onset of jaundice with serum bilirubin ≥3 mg/dl, aspartate aminotransferase (AST) >50 IU/ml and <500 IU/ml, and an AST: alanine aminotransferase (ALT) ratio of >1.5.[1] Additionally, immune, metabolic, viral and other causes of liver disease should be excluded (Fig. 1).

Because of the reluctance of many physicians and patients to obtain a liver biopsy, based on expert recommendation, diagnosis of AH has been stratified as A) *Definite AH*: meeting clinical criteria (alcohol use in excess and laboratory evidence of hepatitis as defined earlier), and confirmation of diagnosis on liver biopsy; B) *Probable AH*: defined when a patient has both alcohol use disorder and hepatitis, and investigations have ruled out other causes of liver disease, including shock or sepsis, or recent cocaine or drug use; and C) *Possible AH*: defined in patients in whom the clinical diagnosis is confounded by i) recent upper gastrointestinal haemorrhage, ischemic hepatitis or drug-induced liver injury, ii) atypical AST and ALT pattern, or iii) uncertainty in the history of alcohol use (Fig. 1). In such patients, a liver biopsy is essential for diagnosis of AH and for inclusion into AH treatment studies.[1]

Key point

Liver biopsy is recommended for diagnosis because up to 30% of patients with a clinical diagnosis of AH may have their diagnosis changed after biopsy.

Role of liver biopsy

The European Association for Study of Liver recommends a liver biopsy to establish a diagnosis of AH,[2] because in up to 30% of patients clinically diagnosed as having AH liver biopsy may lead to an alternative diagnosis.[3,4] In practice, however, liver biopsy is used for definitive diagnosis of AH when the clinical diagnosis is uncertain. Histological diagnosis is based on characteristic histological findings of hepatocyte ballooning, neutrophil infiltrate, Mallory-Denk bodies, together with varying degrees of steatosis and fibrosis, depending on the stage of the disease and the time elapsed from the last alcohol consumption.[5,6] Fibrosis is typically perivenular and pericellular, that is, a "chicken-wire fence" pattern. Central-central and central-portal septa, which are typical of micro-nodular cirrhosis, may be seen.

As the majority of patients with severe AH have ascites and coagulation disorders, the transjugular route is preferred for liver biopsy (Fig. 1). A systematic review confirms the safety of transjugular liver biopsy with a mortality rate of 0.09% and a complication rate of 6.7%.[7] However, the transjugular liver biopsy procedure is not available at many centres, and fear of complications from a percutaneous biopsy limit widespread use of liver biopsy.[8] Liver biopsy may also have a prognostic value. For example, a scoring system based on mega mitochondria, neutrophil infiltrate, cirrhosis and bilirubin stasis helps identify patients at high risk of short-term mortality.[9] The severity of AH based on histology has also been correlated with outcome in an independent study.[4] Further studies are needed to assess whether the findings on histology can be used to determine the choice of therapy or response to treatment.

Unfortunately, we lack accurate non-invasive markers to diagnose AH. Recently, two studies have shown that plasma levels of fragments of cytokeratin 18 may be used for non-invasive diagnosis of AH, but measurement of these fragments has not yet been introduced into clinical practice.[10,11] Similarly, in another translational study, analysing the bioenergetics and mitochondrial function of monocytes in patients with decompensated alcoholic liver disease showed that a reduction in bioenergetics is a potential biomarker for diagnosis of AH.[12,13] Currently, despite some limitations, a liver biopsy is recommended to diagnose AH when the clinical diagnosis is uncertain.[1]

II. What should the protocol be for early diagnosis of infection?

Understanding the pathophysiology of AH and its complications are important to inform diagnostic work-up for infections in patients hospitalised with severe AH.

Pathophysiology of alcoholic hepatitis

Liver injury from alcohol occurs via direct toxicity of the parent compound as well as toxicity of its metabolites. In addition, liver damage occurs indirectly through intestinal dysbiosis from effects of alcohol on the intestines (Fig. 2).[14] The profile of

Please cite this article in press as: Singal AK et al. Grand Rounds: Alcoholic Hepatitis. J Hepatol (2018), https://doi.org/10.1016/j.jhep.2018.05.001