Research Article

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Cirrhosis

Prognosis of treated severe alcoholic hepatitis in patients with gastrointestinal bleeding

Marika Rudler[1], Sarah Mouri[1], Frédéric Charlotte[2], Pascal Lebray[1], Romain Capocci[1], Hedi Benosman[1], Thierry Poynard[1], Dominique Thabut[1,*]

[1]*AP-HP, UPMC, Department of Hepatogastroenterology, La Pitié-Salpêtrière Hospital, 47-80 boulevard de l'Hôpital, Assistance Publique-Hôpitaux de Paris, Pierre et Marie Curie University, 75013 Paris, France;* [2]*AP-HP, UPMC, Department of Anatomopathology, La Pitié-Salpêtrière Hospital, 47-80 boulevard de l'Hôpital, Assistance Publique-Hôpitaux de Paris, Pierre et Marie Curie University, 75013 Paris, France*

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Background & Aims: All trials on severe alcoholic hepatitis (AH) have included patients with "pure" AH, i.e., without concomitant gastrointestinal bleeding (GIB). Severe AH is often suspected in cirrhotic patients with GIB.

We aimed at (1) assessing the prevalence of AH in patients with GIB and Maddrey discriminant function (DF) ⩾32; (2) comparing the outcome in AH patients with or without GIB (AH-GIB+, AH-GIB−); and (3) assessing the performance of the Lille model for survival in AH-GIB+ patients.

Methods: We retrospectively included all patients with alcoholic cirrhosis admitted between January 2005 and March 2011 with the following: (1) jaundice <3 months; (2) DF ⩾32 at admission; (3) bilirubin level >50 μmol/L; and (4) active drinking. Exclusion criteria were advanced hepatocellular carcinoma, other etiology of cirrhosis, severe comorbidities and DF <32 after stabilization. In our centre, we systematically plan a liver biopsy for these patients. Patients with severe AH received prednisolone.

Results: We screened 161 patients (86 GIB+, 75 GIB−), and analyzed data for 58 and 47 patients in each group, respectively. The 2 groups did not differ in prevalence of AH (77.3% *vs.* 81%), demographic data, MELD/Child-Pugh score, or DF. The 2 groups were similar in 6-month probability of survival (73.9 ± 6.0% *vs.* 69.9 ± 7%, $p = 0.49$). The probability of developing infection was lower for AH-GIB+ patients (24.1% *vs.* 44.7%, $p = 0.04$). The AUC for the Lille model in predicting 6-month survival was 0.71 ± 0.06 for all patients and 0.74 ± 0.06 for AH-GIB+ patients ($p > 0.05$).

Conclusions: Prevalence of AH is 80% for patients with cirrhosis and GIB, recent jaundice and DF ⩾32. Infection was lower for AH-GIB+ patients, which suggests a beneficial role of antibiotic prophylaxis treatment. Survival among subjects with GIB was the same as among subjects without GIB.

Introduction

Severe alcoholic hepatitis (AH) is a life-threatening disease with a typical clinical presentation (recent-onset jaundice <3 months, with active drinking and history of long-standing alcoholism), histological definition, and prognosis assessed by Maddrey discriminant function (DF) ⩾32 [1]. International recommendations require the use of glucocorticoids (prednisolone, 40 mg/day) for severe AH [2]. A recent analysis of individual patient data, from 5 randomized controlled trials (RCTs) of corticosteroid treatment, in patients with severe AH [1,3–6], confirmed these recommendations [7]; the treatment was shown to improve 28-day survival. Response to corticosteroid therapy is commonly assessed with the Lille model [8]. Non-response to corticosteroids is highly predictive of sepsis and death [8].

However, all RCTs published in the setting have included patients with "pure" AH, that is, without concomitant gastrointestinal bleeding (GIB). Still, in real life, for patients admitted for GIB, the diagnosis of severe AH is often suspected in those with alcoholic cirrhosis and recent-onset jaundice. Little is known about the prevalence of AH in these patients, prognosis of this subgroup of patients, and efficacy and safety of treatment with corticosteroids. In our centre, we systematically plan a liver biopsy in patients with alcoholic cirrhosis admitted for GIB and who present with a clinical suspicion of severe AH (i.e., recent jaundice and DF ⩾32). When AH is diagnosed, corticosteroids are started, and the Lille model is used to assess response to therapy.

The aims of this study were to (1) assess the prevalence of histologically proven AH in patients with GIB, recent onset of

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* Corresponding author. Address: UPMC, AP-HP, Hôpital Pitié-Salpêtrière, 47-83 bd de l'Hôpital, 75013 Paris, France. Tel.: +33 1 42 16 14 54; fax: +33 1 42 16 14 25.
E-mail address: dominique.thabut@psl.aphp.fr (D. Thabut).

Abbreviations: AH, alcoholic hepatitis; GIB, gastrointestinal bleeding; DF, Maddrey discriminant function; RCTs, randomized controlled trials; INR, International Normalized Ratio.

jaundice, and DF >32; (2) compare features and outcome of AH in patients with and without GIB; and (3) assess the performance of the Lille model for survival in patients with AH and GIB.

Patients and methods

Patients and procedures

We retrospectively included all patients with alcoholic cirrhosis admitted to the hepatology intensive care unit of Pitié-Salpêtrière Hospital, Paris, between January 2005 and March 2011. Inclusion criteria were (1) recent-onset jaundice (<3 months) before hospitalization; (2) DF ⩾32 at admission; (3) total bilirubin level >50 μmol/L at admission; and (4) active drinking and long-term alcoholism. Exclusion criteria were (1) advanced hepatocellular carcinoma; (2) other etiology of cirrhosis (i.e., negative serologic testing for hepatitis B and C and immunodeficiency virus infection); (3) severe comorbidities; and (4) DF <32 after stabilization. We divided patients with histologically proven AH into those with and without upper GIB (AH-GIB+ and AH-GIB−, respectively).

In our unit, liver biopsy is performed via the transjugular route, for all patients with suspected severe AH. AH was histologically defined by the association of neutrophil infiltrate and one of the following features: ballooning or Mallory bodies. Patients with a diagnosis of severe AH receive prednisolone, a single dose of 40 mg/day given intravenously or orally. The Lille score was prospectively assessed in patients after publication of the Louvet *et al.* study [8], and retrospectively evaluated in all patients receiving treatment before publication of the study. Because response to corticosteroids therapy was defined by a Lille score <0.45, corticosteroids were withdrawn in non-responders. In all patients, infection was systematically screened at admission by chest X-ray, ascites testing, and blood and urine culture. In infected patients, antibiotic treatment was administered [8]. Corticosteroids were started at least 48 h after infection was controlled.

Patients were classified as GIB+ if they were admitted to our unit for GIB (i.e., for hematemesis or melena with a bleeding source identified by upper endoscopy). In presence of variceal bleeding, treatment was performed according to Baveno V recommendations [9]. Patients received vasoactive agents (somatostatin or octreotide) after admission and antibiotics for 7 days, and band ligation was performed. In the presence of peptic ulcer bleeding, patients received high-dose proton pump inhibitors for 72 h and double endoscopic treatment was attempted (adrenaline sclerosis and clip placement). Corticosteroids were started after stabilization and effective bleeding control.

Clinical and biologic data

We recorded the following data: age, gender, Child-Pugh score, MELD score, prothrombin time, international normalized ratio (INR) for prothrombin time, serum levels of albumin and creatinine, serum aspartate aminotransferase activity, DF, shock at admission, initial hemoglobin level, and active bleeding at initial endoscopy. Patients were followed up to death or liver transplantation.

Outcomes

Primary outcome was 1-month survival. Secondary outcomes were response to corticosteroid treatment, 3- and 6-month mortality, liver transplantation, and performance of the Lille model for predicting 6-month mortality in AH-GIB+ and AH-GIB− groups.

Definitions

Cirrhosis was defined according to clinical and/or morphological criteria. Infection was defined as positivity for ascites, blood or urine culture on infection screening performed on the day of admission, or clinically evident pulmonary infection or abnormal chest X-ray. Infection at admission was defined by an infection diagnosed on the day of admission. Development of infection was defined as an infection occurring after the beginning of corticosteroid therapy. Rebleeding was defined according to Baveno V recommendations [9]. Response to corticosteroid therapy was defined by a Lille score <0.45.

Statistical analysis

Data are described as mean (range) for quantitative variables and number (percentage) for qualitative variables. Comparisons between groups were assessed by Student's *t* test for quantitative variables and χ^2 or Fisher's exact test for qualitative variables. Survival analysis was performed using a univariate and multivariate Cox model. Patients lost to follow-up were censored as alive at the time of their last visit. Patients who underwent LT were considered as dead at the time of LT. As the Lille and MELD scores are highly correlated, and are two important prognostic indexes, these scores were tested in two different models to avoid multicollinearity. Survival was estimated using the Kaplan-Meier estimator. C-indexes were used to assess the Lille model for 6-month survival. For all analyses, a two-sided p <0.05 was considered statistically significant. Number Cruncher Statistical Systems 2007 (NCSS, Kaysville, Utah, USA) was used for all analyses.

Results

Patients' characteristics

During the study, 161 patients with alcoholic cirrhosis, recent-onset jaundice, and DF ⩾32 were hospitalized in our hepatology unit and therefore considered for liver biopsy. In total, 86 patients presented with GIB (Fig. 1): 3 died before liver biopsy and 5 patients did not undergo biopsy; 1 had advanced hepatocellular carcinoma, and 2 had DF <32 after stabilization. We analyzed data for 75 patients; 58 (77.3%) had AH on liver biopsy, which was performed in a mean delay of 5.4 [1–17] days in the GIB group. Among the 75 patients without GIB, 5 died before liver biopsy, 3 did not undergo liver biopsy, 5 had advanced hepatocellular carcinoma, and 4 had DF <32 after stabilization. We analyzed data for 58 patients, and AH was diagnosed in 47 of them (81%). We included 105 patients with AH: 47 without GIB (AH-GIB−) and 58 with GIB+ (AH-GIB+). Treatment with corticosteroids was started at a median period of 5 days (range 1–6 days), after a bleeding episode.

AH-GIB+ and AH-GIB− patients did not differ in clinical, biological and histological characteristics, except for INR (2.6 ± 0.9 *vs.* 2.1 ± 0.6, p <0.001) and bilirubin level (152 ± 137 *vs.* 206 ± 132 μmol/L, p = 0.02) (Table 1). Shock at admission was more frequent in patients with GIB than without (53.4% *vs.* 12.8%, p <0.001), 5/47 (10.6%) patients were transfused in the AH-GIB− group *vs.* 37/58 (63.8%) in the AH-GIB+ group (p <0.001), but infection at admission did not differ (p = 0.77). In AH-GIB+ patients, the cause of bleeding was variceal bleeding in 34 (58.6%), peptic ulcer in 10 (17.2%), oesophagitis in 7 (12.1%), and other causes in 7 (12.1%). Mean haemoglobin was 8.2 g/dl [3.1–13.5], and 2.8 units of blood were transfused [0–17]. Six patients (10.3%) underwent salvage TIPS in the AH-GIB+ group, and none in the AH-GIB− group.

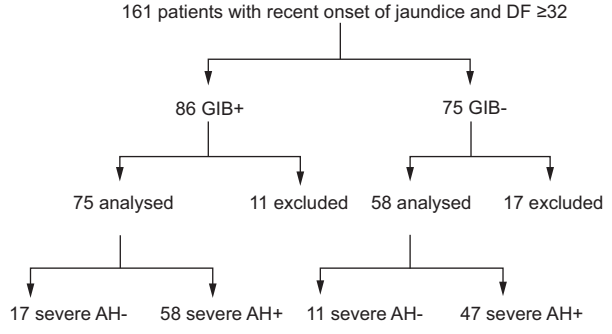

Fig. 1. Patients hospitalised for alcoholic cirrhosis, recent-onset jaundice and discriminant function (DF) ⩾32 (severe alcoholic hepatitis [AH]), with and without gastrointestinal bleeding (GIB).