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RAPID COMMUNICATION

Clinical heterogeneity in autoimmune acute liver failure

Norberto C Chavez-Tapia, Julio Martinez-Salgado, Julio Granados, Misael Uribe, Felix I Tellez-Avila

Norberto C Chavez-Tapia, Julio Martinez-Salgado, Misael Uribe, Felix I Tellez-Avila, Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
Julio Granados, Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
Correspondence to: Norberto Carlos Chávez-Tapia, MD, Departamento de Gastroenterología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga #5. Col. Sección XVI. Del. Tlalpan. C.P. 14000, Distrito Federal, México. khavez@gmail.com
Telephone: +52-54-870900-2710
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Abstract

AIM: To describe the outcome and prognosis in a cohort of patients with acute liver failure due to autoimmune hepatitis without liver transplantation.

METHODS: A retrospective trial was conducted in 11 patients with acute liver failure due to autoimmune hepatitis who attended the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran. Demographic, biochemical and severity indexes, and treatment and outcome were assessed.

RESULTS: Among the 11 patients, with a median age of 31 years, 72% had inflammatory response syndrome, and six patients received corticosteroids. The mortality rate within four weeks was 56%, and the one-year survival was 27%. In the survivors, severity indexes were lower and 83% received corticosteroids.

CONCLUSION: We observed a relatively high survival rate in patients with acute liver failure due to autoimmune hepatitis. This survival rate could be influenced by severity of the disease and/or use of corticosteroids.

Key words: Autoimmune hepatitis; Acute liver failure; Corticosteroids

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INTRODUCTION

Acute liver failure (ALF) is defined as the development of hepatic necrosis with encephalopathy within eight weeks of the onset of liver disease. It is a complex multisystemic event that evolves after a catastrophic insult to the liver ending in the development of a coagulopathy and encephalopathy within a short period of time. ALF is a heterogeneous condition incorporating a range of clinical syndromes[1]. Several etiologies are involved in ALF. However, in the USA and UK, paracetamol, hepatitis A or B and seronegative are the most common ones[2]. The overall mortality varies widely from 10% to 90% in different cohorts. The higher survival rates were observed in those subjects who received liver transplantation, and nowadays ALF accounts for 5%-12% of all liver transplantations[3].

Autoimmune hepatitis (AIH) is an uncommon cause of ALF and is usually associated with type 2 autoimmune hepatitis, particularly in children[4]. In an adult population, AIH occurs in less than 10% of all cases of ALF[5], and acute AIH presents with fulminant hepatic failure and is the last cause of liver transplantation[6]. Few reports about the clinical characteristics and outcomes in this rare group of subjects with ALF are available. Clinically, it is considered a condition that is no longer responsive to corticosteroid therapy or other immunosuppressive therapies[1]. However, Miyake *et al*[7] recently demonstrated in a Japanese population a survival rate of 45% without treatment with corticosteroids. The aim of this study was to describe the clinical outcome and prognoses in a cohort of adult subjects with ALF due to AIH without liver transplantation.

MATERIALS AND METHODS

Subjects

Patients admitted to the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran (Mexico City) for ALF, secondary to AIH, from 1984 to 2004 were studied retrospectively. The autoimmune etiology was defined according to the biochemical and histological criteria of the International Auto-immune Hepatitis Group[8]. Diagnosis of ALF was made according to the previous published criteria[9] which include: the development of hepatic encephalopathy (≥ grade Ⅱ) within eight weeks of the onset of initial symptoms, a prothrombin activity of < 40%, and the absence of previous chronic or alcoholic liver disease. Hepatic encephalopathy was graded on the standard scale of Ⅰ-Ⅳ.

Table 1 Clinical features at time of diagnosis

Case No.	Age (yr)	IAHSS	New onset AIH	BMI (m/kg^2)	HE	SIRS	Bilirubin (mg/dL)	ALT (IU/L)	ALP (UI/L)	INR	Globulin (g/dL)	Creatinine (mg/dL)	ANA	Corticosteroids
[1,3]1	65	17	Yes	31.1	2	Yes	21.9	309	274	1.60	4.1	1.1	1:40	Yes
[1,2]2	17	17	Yes	22.0	3	Yes	15.3	358	136	1.50	2.5	0.9	1:40	Yes
[2]3	66	17	No	20.0	2	Yes	8.4	31	207	1.50	4.4	0.9	1:80	Yes
[1,2]4	28	17	Yes	30.3	2	Yes	22.9	128	262	1.90	5.7	1.1	1:80	Yes
[1,2]5	52	14	Yes	27.5	2	No	21.2	217	186	1.90	4.5	0.6	1:40	No
[1]6	17	20	Yes	22.5	2	No	7.6	414	271	1.70	7.7	0.8	1:80	Yes
7	31	18	No	19.9	4	Yes	22.0	541	138	3.60	2.9	6.6	1:80	Yes
8	25	14	No	35.0	3	Yes	26.8	23	309	1.90	3.1	2.7	1:40	No
[1,3]9	67	13	Yes	26.9	2	No	13.8	683	135	8.12	2.4	2.3	1:80	No
10	18	12	Yes	27.0	3	Yes	22.6	126	120	2.20	2.7	1.1	1:40	No
11	33	13	Yes	23.3	3	Yes	20.1	173	199	3.60	4.3	1.4	1:80	No

IAHSS: international autoimmune hepatitis scoring system; HE: hepatic encephalopathy grade; SIRS: systemic inflammatory response syndrome; ALT: alanine aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; ANA: antinuclear antibody; BMI: body mass index. [1]Cases treated with corticosteroids, [2]Cases that survived one month, [3]Cases that survived more than three years.

Other etiologies were excluded by the absence of IgM anti-hepatitis A virus antibody, IgM anti-hepatitis B virus core antibody or hepatitis B surface antigen. In addition, drug-related disease, acute fatty liver of pregnancy, ischaemic hepatitis, Wilson's disease, malignant infiltration, cytomegalovirus, Epstein-Barr virus and herpes simplex were also excluded.

Baseline clinical characteristics such as age, gender, and body mass index were recorded; similar biochemical values, and Acute Physiology And Chronic Health Evaluation score[10], systemic inflammatory response syndrome[11] and multiple organ failure were assessed[12]. Mortality was classified as either in-hospital and out-hospital.

Statistical analysis

All statistical analyses were carried out with the SPSS/PC v 10.0 program (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed in terms of median and range. Statistical significance was set at $P < 0.05$. Variables were analysed using the exact Fisher's test (two-tailed), Mann–Whitney *U* test and 95% confidence intervals.

RESULTS

Among 58 subjects with ALF, AIH was the etiology (19%) in 11 cases. All cases had onset of encephalopathy within 28 days, and all were not diagnosed previously with AIH. Ten were females (90.9%), with a median age of 31 years (range, 17-67 years) and mean body mass index of 25 ± 4 m/kg^2. Liver biopsy was performed in eight subjects to determine the diagnosis. Eight subjects (72%) had systemic inflammatory response syndrome. The baseline biochemical values were: bilirubin 18.4 ± 6.2 mg/dL, alanine aminotransferase 273 ± 219 U/L (median, 273; range, 31-683), alkaline phosphatase 203 ± 67 U/L, international normalized ratio 2.6 ± 1.95 (median, 1.9; range, 1.5-8.12) and creatinine 1.77 ± 1.72 mg/dL (median, 1.1; range, 0.6-6.6) (Table 1). The overall mortality was 54.5% ($n = 6$); however, only 16.6% (1/6) of these subjects received corticosteroids. Corticosteroid was used based on the initial clues that indicated AIH as a cause of ALF. Additionally, all patients were treated with maximal available supportive care according to their clinical characteristics.

In-hospital mortality was 45.4% ($n = 5$), the one-month survival rate was 54% ($n = 6$), with three subjects (27%) surviving more than one year, and the longest follow-up being six years.

When the subjects were analysed according to death/survival, differences were observed in the prevalence of severe hepatic coma, APACHE Ⅱ score, SIRS, sepsis, severe sepsis, and multiorgan failure at baseline (Table 2).

Those subjects who survived more than three years (cases 1, 2 and 9) had similar characteristics, except for age, creatinine and INR at presentation. The three subjects received corticosteroids: 1 g/d methylprednisolone i.v. for three days, followed by hydrocortisone 100 mg i.v. until enteral feeding was available, when 40 mg prednisone was administered. Cases 1 and 9 had the longest follow-up for six years, and in case 1 all drugs were withdrawn at four years of follow-up without additional liver function tests; case 2 was followed for four years, and at the last visit, treated with 50 mg/d azathioprine; and case 9 continues to be treated with prednisone.

DISCUSSION

Although liver transplantation can improve the outcome in ALF, the overall mortality without liver transplantation is still high[13]. In this study, we presented the clinical experience of one single referral hospital in subjects with AIH and ALF.

These findings are particularly interesting, because we observed a higher prevalence of AIH (about 20%) compared to other reports[7,14]. Information about AIH in ALF is scarce. Recently, Miyake *et al*[7] in a Japanese study reported the clinical characteristics in 11 subjects with fulminant AIH. Contrary to our study, their response rate to corticosteroids without transplantation was low (two of seven subjects), and an unexpectedly high survival rate was observed in those with supportive treatment.

In recent years, a better response in subjects with ALF has been observed. At least two studies showed higher survival rates (a three-week survival rate without

Table 2 Clinical features at d 1 of survivors and non-survivors

Variables	In-hospital survival (n = 6) median (range)	In-hospital non-survival (n = 5) median (range)	P
Age (yr)	52 (17-67)	29.5 (18–66)	0.43
HE grade (Ⅲ or Ⅳ), n (%)	1 (16)	4 (80)	0.10
Body mass index (m/kg^2)	26.9 (22–31.1)	25.1 (20–35)	0.39
APACHE score	8 (6–13)	20 (11–23)	0.08
Total bilirubin (mg/dL)	15.3 (7.6–21.9)	22.3 (8.4–26.8)	0.35
Alanine aminotransferase (IU/L)	358 (217–683)	127 (23–541)	0.35
INR	1.7 (1.5–8.12)	2.05 (1.5–3.6)	0.35
Creatinine (mg/dL)	0.9 (0.6–2.3)	1.25 (0.9–6.6)	0.20
Serum sodium (mEq/L)	134 (131–138)	134 (125–149)	0.35
SIRS (yes), n (%)	0	1 (20)	0.45
Sepsis (yes), n (%)	1 (16)	2 (33.2)	0.42
Severe sepsis (yes), n (%)	1 (16)	3 (60)	0.19
Septic shock (yes), n (%)	0	0	NS
Multiple organic failure (yes), n (%)	0	5 (100)	0.02
Corticosteroids (yes), n (%)	5 (83)	1 (20)	0.06

HE: hepatic encephalopathy grade; APACHE: acute physiology and chronic health evaluation; SIRS: systemic inflammatory response syndrome.

liver transplantation is 80% in the Miyake *et al*[7] study and 54% at a four-week survival in our study) compared with one initial report (a three-week survival rate without liver transplantation was approximately 20%). In fact, the mortality rate observed in all cases of ALF in our institution was 49%[15]. However, we observed a lower mortality rate at one month (only with statistic tendency) in subjects who received corticosteroids (18% *vs* 80% in those without corticosteroids), but survivors showed lower values of severity at baseline. We observed a trend of better prognosis in those subjects treated with corticosteroids. This could be explained by the fact that since this therapy is oriented to pathophysiological process involved in the etiology of ALF, only supportive management was offered due to lack of transplantation.

Unfortunately, due to the low number of subjects in reported series[16,17], it is difficult to establish more categorical conclusions about therapeutic interventions, and prospectively controlled trials using corticosteroids are unethical, particularly when the majority of subjects with acute AIH present with fulminant hepatic failure[18].

In subjects with ALF due to AIH, many pathogenic events occur; for instance, an important loss of homeostasis with multiorgan failure as the main outcome, includes an uncontrolled immune response. Although liver transplantation is considered the best treatment of choice in ALF, it is not always available in all centres, and the clinical usefulness of other non-surgical options directed to pathogenic mechanisms has not been fully explored.

Corticosteroids are considered the main treatment of AIH, but their side-effects are often significant. In the clinical scenario of acute liver failure, the study of Harry *et al*[19] demonstrated that the use of high doses of corticosteroids in subjects with hypotensive acute liver failure (none with AIH) could help reduce noradrenaline requirements after 48 h with steroid therapy. However, no differences were observed in survival, but length of intensive care unit stay was prolonged in the steroid-treated group, increasing the length of waiting time for a suitable organ donor. Unfortunately, the incidence of infection due to resistant organisms such as Candida albicans was high in this group.

In conclusion, we observed in a cohort of subjects from a clinical setting where transplantation is not feasible, a relatively high clinical heterogeneity of ALF due to AIH that showed a high survival rate. These observations may be influenced by both severity of the disease and the use of high doses of corticosteroids.

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