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CLINICAL STUDIES OF RESISTANT ASCITES IN LIVER CIRRHOSIS

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Abstract. Resistant ascites was studied in 34 patients with liver cirrhosis and ascites. The patients were initially divided into 3 groups on the basis of the weekly cumulative ascites retention curve : patients relieved of ascites within 3 weeks of admission, patients relieved between 4 and 12 weeks and patients with ascites persisting beyond 13 weeks. "Resistant ascites" was defined as "ascites persisting for more than 13 weeks after admission to the hospital". The patients were then reclassified into 3 groups : Group A being those patients relieved of ascites within 12 weeks, Group B being those with resistant ascites and group C being those who died within 12 weeks of admission. There were no differences in age and sex distribution, etiology of liver cirrhosis, past medical history or physical findings among the 3 groups. However, Group B had higher levels of serum creatinine and blood urea nitrogen than Group A on admission. Serum bilirubin was higher and serum albumin was lower in Group C than in Group B, which indicates that Group C had greater liver cell failure.

Key words : liver cirrhosis, hepatic ascites, resistant ascites.

The presence of ascites in patients with liver cirrhosis indicates that their liver is decompensated, and it is known as a sign of poor prognosis (1-3). Therefore, treatment of ascites is important, but, although treatment has improved (4), ascites resistant to treatment remains. The cause of resistant ascites is not well known (5).

In this paper, the authors classified patients with liver cirrhosis and ascites into 3 groups on the basis of the weekly cumulative ascites retention curve and compared clinical findings among the 3 groups in order to characterize resistant ascites.

SUBJECTS AND METHODS

Subjects. Thirty-four patients with ascites were selected from 215 patients with liver cirrhosis who were admitted to our department during the 5-year period from January 1974 to December 1978. Ascites was diagnosed by physical examinations. One of the patients was admitted twice with ascites during the period, and both admissions were included in the study.

The age and sex distributions are shown in Table 1. Liver cirrhosis was diagnosed by laparoscopy and liver biopsy in 14 patients, by autopsy or histological examination of the liver

tissue obtained after death in 14 patients, and by clinical findings in 6 patients. Patients with hepatocellular carcinoma were excluded.

Methods. The weekly cumulative survival rate and the weekly cumulative ascites retention rate were calculated by the life table method (6). On the basis of the weekly cumulative ascites retention curve (Fig. 2), the patients were classified into 3 groups. Group A consisted of 16 patients whose ascites disappeared within 12 weeks of admission. All of them were discharged. Group B consisted of 8 patients whose ascites persisted for more than 13 weeks after admission. Two of them were discharged, but 6 died in the hospital. Group C consisted of 10 patients who died within 12 weeks.

Fifty parameters shown in Tables 2-5 were compared among the 3 groups. In Groups A and C, physical findings and laboratory data on admission were compared with those at the time of disappearance of ascites or at the time of death. Retention and disappearance of ascites were decided by physical examination by the doctor in charge. The duration of ascites retention was defined as the time from admission to the time of disappearance of ascites or to the time of death. The duration of ascites retention before admission was not taken into account.

The urine volume and specific gravity were recorded as average weekly values. HBs antigen was measured by immunoelectrophoresis from 1974 to 1977 and by reversed passive hemagglutination thereafter. Protein concentration of the ascitic fluid was measured with a refractometer.

All results were shown as the mean ± standard deviation, except for the serum total and direct bilirubin, GOT, GPT, alkaline phosphatase, blood ammonia, BUN, serum creatinine, urinary sodium, urinary chloride, urinary potassium and urinary sodium excretion values which were converted to logarithms before treating statistically. After converting to the antilogarithms, the data were expressed as the mean-SD — mean + SD. All data were treated by the t test, the paired t test or the chi-square test using the Yates modification.

RESULTS

Weekly Cumulative Survival Rate

The weekly cumulative survival rate decreased gradually to 71 % until the 7 th week of admission, and remained at almost the same level thereafter (Fig. 1). Sixteen patients (47 %) died in the hospital. The causes of death of 10 of the patients who died within the first 7 weeks were gastrointestinal hemorrhage (8 patients) and renal failure (2 patients). The causes of death of the 6 patients who

TABLE 1. AGE AND SEX DISTRIBUTION OF PATIENTS WITH LIVER CIRRHOSIS AND ASCITES

Age	Male	Female	Total
20-29	1	0	1
30-39	2	0	2
40-49	14	1	15
50-59	10	2	12
60-69	2	2	4
Total	29	5	34

died after the 7 th week were hepatic coma (3 patients), shock other than hemorrhagic shock (2 patients) and gastrointestinal hemorrhage (1 patient).

Weekly Cumulative Ascites Retention Rate.

The weekly cumulative ascites retention rate was 62 % at the 4 th, 44 % at the 8 th, 33 % at the 12 th, 28 % at the 16 th, 28 % at the 20 th, 21 % at the 24 th and 10 % at the 28 th week (Fig. 2). The 50 % retention rate was at 7 weeks. The retention curve was divided into 3 linear sections : a rapid fall during the 1st-3rd week, a gradual fall during the 4 th-12 th week and almost no change

TABLE 2. COMPARISON OF AGE, SEX, ETIOLOGICAL FACTORS OF LIVER CIRRHOSIS AND PAST MEDICAL HISTORY AMONG THE 3 GROUPS

	Group A	Group B	Group C
No. of cases	16	8	10
Age	50.8± 8.5 (34-65)	54.1± 5.6▲ (48-64)	45.1± 10.2▲ (23-59)
Sex Male	13 (81%)	6 (75%)	10 (100%)
Female	3 (19%)	2 (25%)	0
Etiological factors			
Alcoholics (Al)	9 (56%)	6 (75%)	4/9 (44%)
HBs antigen (HBsAg)	2 (13%)	1 (13%)	4/8 (50%)
Al HBsAg			
+ +	1 (6%)	1 (13%)	1 (14%)
+ −	8 (50%)	5 (63%)	2 (29%)
− +	1 (6%)	0	3 (43%)
− −	6 (38%)	2 (25%)	1 (14%)
Past medical history			
Ascites (AS)	5 (31%)	4 (50%)	4 (40%)
Once	4	3	3
Twice	1	1	1
Hepatic encephalopathy (HE)	2 (13%)	2 (25%)	2 (20%)
Once	1	2	1
Twice	1	0	1
Gastrointestinal hemorrhage (GIH)	2 (13%)	1 (13%)	0
Once	2	1	0
AS HE GIH			
+ + +	1 (6%)	0	0
+ + −	1 (6%)	0	2 (20%)
+ − +	1 (6%)	0	0
− + +	0	1 (13%)	0
+ − −	2 (13%)	4 (50%)	2 (20%)
− + −	0	1 (13%)	0
− − −	11 (69%) ○	2 (25%) ○	6 (60%)
+ or + or +	2 (13%) ●	5 (63%) ●	2 (20%)

▲ ● : $p < 0.05$, ○ : $p < 0.01$

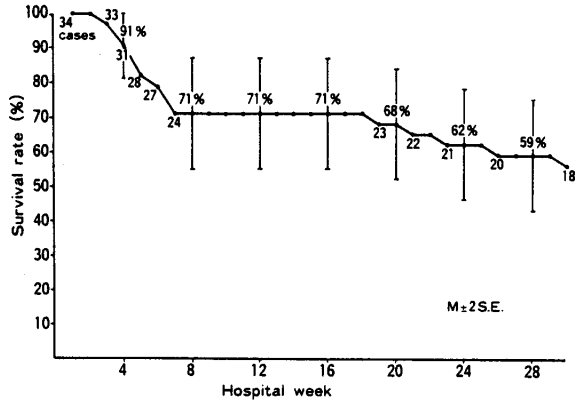

Fig. 1. Weekly cumulative survival rate in liver cirrhosis with ascites (Number indicates survived cases.)

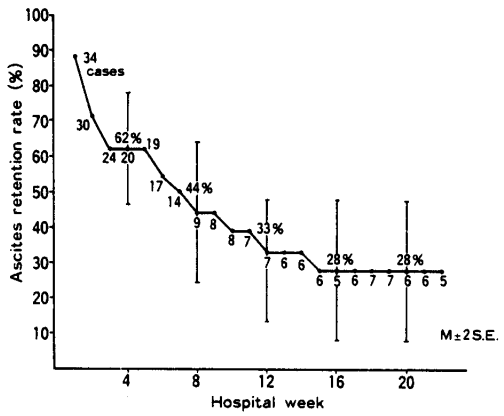

Fig. 2. Weekly cumulative ascites retention rate in liver cirrhosis with ascites (Number indicates cases with ascites.)

after 13 weeks. As described in Methods, these results were used to classify the cases into 3 groups.

Eighteen patients (53 %) were relieved of ascites after 1-24 weeks (median, 3 weeks) and discharged from the hospital. Eleven patients (32 %) had ascites throughout their stay in the hospital until death. The duration of ascites retention, or from admission to death, in these patients was 3-30 weeks (median, 5 weeks). In 5 patients (15 %), ascites disappeared temporarily in the hospital but reappeared afterwards. The duration of the first ascites retention was 1-27 weeks (median, 7 weeks), and the ascites-free period was 3-43 weeks (median, 7 weeks). The duration of the 2 nd ascites retention until death was 2-15 weeks (median, 3 weeks).

Comparison of Clinical Results among Groups A, B and C

Age and sex. There was no difference in age except that Group C was younger than Group B by 9 years. There were no statistically significant differences among the 3 groups in sex distribution (Table 2).

TABLE 3. COMPARISON OF PHYSICAL FINDINGS ON AND AFTER ADMISSION AMONG THE 3 GROUPS

	Group A	Group B	Group C
No. of cases	16	8	10
Jaundice			
On admission	5 (31%)□	3 (38%)▲	10 (100%)▲□
After admission	3 (19%)□	3 (38%)▲	10 (100%)▲□
Peripheral edema			
On admission	8 (50%)	4 (50%)	6 (60%)
After admission	2 (13%)	2 (25%)	5 (50%)
Hepatic encephalopathy			
On admission	0	1 (13%)	1 (10%)○
After admission	1 (6%)□	4 (50%)▲	10 (100%)□▲○
Gastrointestinal hemorrhage			
On admission	0	0	1 (10%)○
After admission	0□	2 (25%)	8 (80%)□○
Vascular spider	9 (56%)	6 (75%)	6 (60%)
Pleural effusion	1 (6%)	1 (13%)	2 (20%)
Hepatomegaly	10 (63%)	3 (38%)	4/8 (50%)
Splenomegaly	7 (44%)	3 (38%)	4/8 (50%)

▲ : $p < 0.05$, ○□ : $p < 0.01$

Etiological factors of liver cirrhosis. Patients who had ingested more than 80 g of ethanol per day for more than 10 years were classified as having a positive history of alcohol ingestion (7) (Table 2). The 3 groups showed no differences in having a history of alcohol ingestion or being positive for HBs antigen.

Past medical history. There were no differences among the 3 groups in having histories of ascites, hepatic encephalopathy or gastrointestinal hemorrhage. Patients of Group B more often suffered from such problems than those of Group A, but there were no differences in other comparisons (Table 2).

Physical findings on and after admission. The incidences of jaundice, peripheral edema, hepatic encephalopathy, gastrointestinal hemorrhage, vascular spider, pleural effusion, hapatomegaly and splenomegaly in the 3 groups were compared. On admission, jaundice was more frequent in Group C than in Groups A and B (Table 3). There were no differences in other physical findings among the 3 groups. During hospitalization, there were no differences between Groups A and B. However, jaundice and hepatic encephalopathy were more frequent in Group C than in Group B, and jaundice and gastrointestinal hemorrhage were more frequent in Group C than in Group A.

Laboratory data on admission. BUN and serum creatinine were more elevated in Group B than in Group A. Direct bilirubin was higher and serum albumin was lower in Group C than in Group B. Serum bilirubin, serum γ-globulin and BUN were higher, but serum albumin was lower in Group C than in Group A.

TABLE 4. COMPARISON OF LABORATORY DATA, ON ADMISSION AMONG THE 3 GROUPS, ON ADMISSION AND AT THE TIME OF DISAPPEARANCE OF ASCITES IN GROUP A, AND ON ADMISSION AND AT THE TIME OF DEATH IN GROUP C

	Group A A	Group A A′	Group B B	Group C C	Group C C′	A vs. B	B vs. C	A vs. C	A vs. A′	C vs. C′
No. of cases	16	16	8	10	10					
Liver function tests										
Total bilirubin (mg/dl)	1.4, 0.6-3.5	1.5, 0.9-2.8	2.0, 1.2-3.3	3.9, 1.6-9.4	9.1, 3.9-21.2			<		≪
Direct bilirubin (mg/dl)	0.7, 0.3-1.8	0.8, 0.4-1.6	0.5, 0.5-0.6	1.8, 0.5-6.2	5.1, 1,9-14.1		<	<		<
GOT (K. u)	85, 53-134	95, 56-163	73, 46-116	103, 55-192	134, 69-260					
GPT (K. u)	55, 28-110	64, 31-133	47, 23-97	61, 32-118	77, 31-188					
Choline esterase (ΔpH)	0.44 ± 0.15	0.48 ± 0.14	0.39 ± 0.15	0.32 ± 0.17	0.33 ± 0.16					
Cholesterol (mg/dl)	156 ± 38	168 ± 48	145 ± 46	123 ± 47	119 ± 47					
ZTT (K. u)	11.9 ± 2.3	12.6 ± 2.5	13.9 ± 3.1	13.8 ± 3.5	12.3 ± 3.7					
Blood ammonia (μg/dl)	103, 60-176	141, 77-257	110, 70-174	122, 80-185	168, 106-266					
Total protein (g/dl)	6.3 ± 0.8	6.7 ± 0.8	6.5 ± 0.8	6.1 ± 0.5	5.5 ± 0.5				<	≪
Albumin (g/dl)	2.9 + 0.5	3.1 + 0.4	3.0 + 0.5	2.4 + 0.3	2.9 + 0.4		≫	>	<	<
γ-globulin (g/dl)	2.0 + 0.4	2.3 + 0.7	2.2 + 0.7	2.6 + 0.7	1.8 + 0.3			<		≪
Prothrombin time (sec.)	15.0 ± 1.2	16.9 ± 1.2	16.8 ± 3.3	17.5 ± 3.4	18.7 ± 3.2					≪
Renal function tests and electrolytes										
Urine volume (ml/day)	1,350 ± 530	1,340 ± 420	1,160 ± 190	1,250 ± 550	920 ± 410					
Urine specific gravity	1,018 ± 5	1,017 ± 5	1,020 ± 1	1,018 ± 5	1,020 ± 4					
BUN (mg/dl)	12, 7-19		19, 16-23	23, 11-46	57, 19-169	<		<		≪
Serum creatinine (mg/dl)	1.00, 0.98-1.03		1.26, 1.11-1.44	1.30, 0.87-1.93	2.68, 1.13-6.35	<				
Serum Na (mEq/l)	136 ± 3	134 ± 3	136 ± 3	133 ± 5	130 ± 10				>	
Serum Cl (mEq/l)	103 ± 4	104 ± 5	103 ± 5	104 ± 7	97 ± 8					>
Serum K (mEq/l)	4.0 ± 0.4	4.5 ± 0.7	3.9 ± 0.3	4.1 ± 1.0	4.5 ± 0.7				<	
Urine Na (mEq/l)	63, 35-114		73, 44-119	57, 22-150	25, 8-75					
Urine Cl (mEq/l)	60, 32-111		74, 23-242	77, 36-164	35, 16-74					
Urine K (mEq/l)	22, 14-35		31, 24-41	29, 19-42	34, 23-50					
Urine Na excretion (mEq/day)	97, 52-182		85, 41-176	58, 18-186	22, 6-80					
Urine protein ≫ +	1 (6%)	0	2 (25%)	1 (10%)	2 (20%)					
Urine sediment, RBC ≫ 5/hpf	2 (13%)	1 (6%)	2 (25%)	1 (10%)	2 (20%)					
Urine cast ≫ +	0	0	0	3 (30%)	5 (50%)					
Others										
Hematocrit (%)	34.2 ± 4.5	34.3 ± 2.9	35.5 ± 6.3	35.3 ± 6.6	28.8 ± 5.9					>
Fasting blood glucose (mg/dl)	149 ± 101	148 ± 55	125 ± 36	118 ± 37	155 ± 69					<
Ascites protein conc. (g/dl)	1.1, 0.5-2.4		1.0, 0.4-2.5	0.7, 0.3-1.3						

A, B, C : On admission, A′ : At the time of disappearance of ascites, C′ : At the time of death, < > : $p < 0.05$, ≪ ≫ : $p < 0.01$

TABLE 5. COMPARISON OF TREATMENTS AMONG THE 3 GROUPS

	Group A	Group B	Group C
No. of cases	16	8	10
Daily NaCl intake			
2-5 g	10 (63%)	6 (75%)	10 (100%)
6-10 g	6 (38%)	2 (25%)	0
Diuretics			
S F P			
+ − −	8 (50%)	1 (13%)	1 (10%)
+ + −	7 (44%)●■	1 (13%)●	1 (10%)■
+ − +	0	0	1 (10%)
+ + +	1 (6%)○□	6 (75%)○	7 (70%)□
Plasma infusion	1 (6%)○□	6 (75%)○	8 (80%)□
Blood transfusion	0●□	3 (38%)●	7 (70%)□
Steroids	0	0	3 (30%)
Ascites reinfusion	0	2 (25%)	2 (20%)

S : Spironolactone, F : Furosemide, P : Plasma infusion, ■●: $p < 0.05$, □○ : $p < 0.01$

(Table 4).

Therapy. There was no difference in therapy between Groups B and C. Patients were more frequently treated with blood transfusion, combination of spironolactone and furosemide, and/or plasma infusion in Groups B and C than in Group A (Table 5). Steroids were administered to 3 patients in Group C, and ascites reinfusion was performed in 2 patients each of Groups B and C.

Comparison of the Clinical Data on Admission with Those at the Time of Disappearance of Ascites in Group A.

There were no differences in the physical findings. Serum protein, albumin and potassium were higher at the time ascites disappeared than on admission, whereas serum sodium was lower (Tables 3, 4).

Comparison of Clinical Data at the Time of Death with Those on Admission in Group C.

Hepatic encephalopathy and gastrointestinal hemorrhage were more often obesrved at the time of death than on admission (Table 3). Serum bilirubin, albumin, BUN and fasting blood glucose were higher, while serum protein, γ-globulin, chloride, and hematocrit were lower upon death than on admission (Table 4).

DISCUSSION

Definition of resistant ascites. The definition of resistant ascites has been under change and is confused, because new therapies have appeared with the passage of time. Previous definitions were derived from roughly three bases : duration of ascites retention (2, 8-10), response to treatment (11), and laboratory

data in addition to the above (12).

In terms of the duration of ascites retention, resistant ascites has been defined as that which does not disappear even after treatment for 1-3 months as an in-patient (8, 9), or as the ascites in which effective diuresis does not occur even after 10 days to 3 weeks of hospitalization (2, 10). In terms of the response to therapy, resistant ascites has been defined as that which persists despite of the combined use of a low salt diet, spironolactone and loop diuretics (11). By laboratory data in addition to both of the above, resistant ascites has been defined as the case in which no loss of body weight occurs even several weeks after admission, the urinary sodium concentration is less than 5 mEq/l and urinary sodium excretion is less than 30 mEq/day after administration of 200 mg/day of hydrochlorothiazide (12).

The weekly cumulative ascites retention curve determined in our study could be divided into 3 straight line periods : a rapid fall from the 1st to 3rd week, a gradual fall from the 4th to 12th week, and a period of almost no change in the ascites retention rate after 13 weeks. In view of these results, resistant ascites was defined as that which lasts more than 13 weeks after admission to the hospital (Group B). The results coincide as to duration with those of Blendis *et al.* (9), though the basis of their definition of resistant ascites is not well detailed.

It was difficult to decide whether the patients in Group C that died within 12 weeks of admission had resistant ascites, as they died before the 13th week.

The incidence of resistant ascites in this study was 24 % which is higher than the 5-6 % reported in previous papers (13, 14), probably because of differences in sampling of patients or the definition of resistant ascites.

Comparison of the cases of resistant ascites and reactive ascites. Comparison of the clinical data on admission between cases of resistant ascites (Group B) and cases of reactive ascites (Group A) showed no significant differences in age, sex, etiology of liver cirrhosis or physical findings. In the laboratory data, however, BUN and serum creatinine levels were higher in Group B than in Group A, that is, renal function was worse in the former. These results coincide with the statement of Conn (14) concerning how difficult it was to differentiate between resistant ascites and the hepatorenal syndrome. On the other hand, Group C had higher serum indirect bilirubin and less serum albumin from the time of admission than Group B. Liver cell failure was evident and greater in Group C than the other groups. Many patients of Group C had gastrointestinal hemorrhage and hepatic encephalopathy during their hospital course. These results indicate that the present classification of the cases of ascites is appropriate and useful for clinical studies. Kawasaki *et al.* reported that the incidence of jaundice, oliguria and hypoalbuminemia were high in patients with diuretic resistant ascites (15). Gabuzda reported that patients with diuretic resistant ascites had marked ascites, had no edema, and many had hypoalbuminemia and hyponatremia (16). These reports might have included cases similar to those in Group C of the present study.

Prognosis of patients with liver cirrhosis and ascites. Prognosis of patients with liver cirrhosis has been studied with regard to the etiology of liver cirrhosis, past medical history, present illness, liver function tests, laparoscopy and liver biopsy findings (1-3, 17-19). The presence of ascites has been the most definite determinant of the prognosis of liver cirrhosis. The survival rate of patients having had ascites for 1, 3 and 5 years was reported by Okazaki *et al.* (18) to be 70 %, 44 % and 12 %, respectively. The 6 month survival rate in the present study was 60 %, which is not significantly different from the rates of Okazaki *et al.* (82 %, 18) and of Miwa *et al.* (58 %, 19). The survival curve (Fig. 1.) of patients with liver cirrhosis and ascites in the present study showed that the majority of the deaths occurred within the first 7 weeks of admission. Deaths decreased after 2 months. Hapatic cell dysfunction was marked in the patients who died.

Most researchers agree that patients with resistant ascites have a poor prognosis. For example, Sherlock reported that 9 patients with resistant ascites out of 157 patients with ascites died within 6 months (13). Six out of the 8 of the present patients with resistant ascites died in the hospital (19-85 weeks after admission).

Recently, ascites reinfusion and the peritoneovenous shunt have been reported to be effective in the treatment of resistant ascites (20, 21). Ascites reinfusion did prove effective in 2 of our patients. The definition of resistant ascites may change again as new therapies to treat it effectively are developed.

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