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Original Articles

Nutritional status in non-alcoholic sub-clinical porto-systemic encephalopathy

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Subject headings liver cirrhosis; portal-systemic encephalopathy; nutritional status; albumin; somatosensory evoked potentials

Abstract

AIM: To understand the role of nutritional status in cirrhotic patients without clinical porto-systemic encephalopathy (PSE).

METHODS: Fifty-one non-alcoholic patients with cirrhosis without PSE were studied prospectively and compared with 20 healthy volunteers. The nutritional evaluation included serum prealbumin, albumin, transferrin, body mass index (BMI), mid-arm muscle circumference (MAMC), and grip power. The occurrence of subclinical PSE (SPSE) was defined when N20 - N65 inter-peak latencies of median nerve-stimulated somatosensory evoked potentials were > 2.5 standard deviations of control means. Blood chemistries were tested within 12h of somatosensory evoked potentials test and nutritional evaluation.

RESULTS: Twenty-five, 17 and 9 cirrhotic patients were graded as Child-Pugh class A, B, and C, respectively. Twenty-four (47.1%) patients developed SPSE. Cirrhotic patients with SPSE had lower serum albumin (2.8 mg/L ± 5 mg/L *vs* 31 mg/L±7 mg/L, $P<0.001$) levels than those without SPSE. Prealbumin (106mg/L ±57mg/L *vs* 125 mg/L ±58 mg/L), transferrin (1.64 g/L ± 0.46 g/L *vs* 1.78 g/L±0.58 g/L), BMI (23.7 kg/m^2 ± 2.7 kg/m^2 *vs* 25.3 kg/m^2 ± 3.6 kg/m^2), MAMC (22.2 cm ± 2.6 cm *vs* 22.7 cm ±3.5 cm), and grip power (26.3 kg ± 6.4 kg *vs* 26.9 kg ± 6.8 kg) were not different between cirrhotic patients with and without SPSE. N20-N65 inter-peak latencies were correlated with serum albumin levels ($P = 0.01$) but not with prealbumin, transferrin, BMI, MAMC, or grip power. Serum albumin, prealbumin and transferrin levels were different among cirrhotic patients with Child-Pugh classes A, B, and C ($P <0.05$). BMI, MAMC, and grip power were not different among Child-Pugh classes A, B and C.

CONCLUSION: Our data suggest that serum albumin level is a simple test in the evaluation of nutritional status in patients with cirrhosis.

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INTRODUCTION

Protein-calorie malnutrition is common in patients with cirrhosis[1-4]. Many factors, including reduced nutrient ingestion, malabsorption, increased demand of mutrients, and alteration of energy metabolism have been suggested as a cause of malnutrition in cirrhotic patients[2]. In patients with cirrhosis, malnutrition may increase the number of complications and deteriorate liver functions[1]. Malabsorption can result in muscle wasting, amino acid imbalance, hypoalbuminemia, and zinc deficiency, which are thought to be involved in the pathogenesis of portosystemic encephalopathy (PSE)[5].

In our previous studies, N20-N65 inter-peak latencies (IPLs) of somatosensory evoked potentials (SEPs) were useful in the detection and monitoring of PSE[6-8]. The SEPs in patients with chronic liver disease without clinical PSE showed minimal dysfunction in central and peripheral conduction, with delayed peak and inter-peak latencies (IPLs)[7-10]. In patients with cirrhosis, malnutrition and increased circulating toxic substances may result in diffuse neuropathy[11,12]. Our subsequent study showed that N20-N65 IPLs of SEPs were helpful in the assessment of subclinical PSE (SPSE), and about a half of cirrhotic patients had SPSE[13]. The role of nutritional status in cirrhotic patients with SPSE remains uncertain. Thus, we conducted this study.

PATIENTS AND METHODS

We prospectively studied 51 documented patients (mean age: 58±11 years; 29 men, 22 women) with non-alcoholic cirrhosis (hepatitis B virus, 24; hepatitis C virus, 23; hepatitis B virus and hepatitis

C virus, 2; hepatitis B virus and hepatitis D virus, 1; cryptogenic, 1) without clinical PSE at the Cathay General Hospital from 1995 through 1997. Twenty healthy volunteers served as control subjects. Cirrhosis was diagnosed when a patient developed chronic hepatitis, sonographic findings of small liver as well as splenomegaly, and the presentation of moderate or severe degrees of esophageal varices. Chronic hepatitis was defined when serum alanine aminotransferase (ALT) levels were 1.5 times higher than the upper normal limit (normal ALT activity <35 IU/L) over a period of more than 6 months.

Patients with neurological diseases and metabolic disorders such as alcoholism, diabetes mellitus and end-stage renal disease were excluded to avoid coexistent neuropathy or other brain dysfunction. Patients with fever, sepsis or shock were also excluded to avoid variations caused by body temperature. All cirrhotic patients had blood tests and were tested for grading of PSE and SEPs.

The degree of PSE of each patient was semiquantified into grades from 1 to 4, based on the mental changes proposed by Conn[14] immediately prior to the SEP test. The SEP recordings were carried out in a quiet and dimly lit room with the subjects in a supine position using a Dantec Counterpoint (Dantec Elektronik Medicinsk, Skovlunde, Denmark) by a method as described in previous studies[6,13]. Median nerve evoked cortical responses were recorded for N20-N65 inter-peak latencies (IPLs). The occurrence of SPSE in cirrhotic patients was defined when N20-N65 IPLs of median nerve stimulated SEPs were greater than 2.5 of standard deviations of control means.

For the assessment of nutritional status, biochemical analyses and anthropometric measurements were made within 4h of SEP test. Biochemical analyses included serum prealbumin, albumin and transferrin levels. Anthropometric measurements included weight, height, mid arm circumference (MAC), triceps skin fold (TSF) and mean grip power taken by the same dietitian[15]. The body mass index (BMI, kg/m^2) was calculated using the equation: BMI = weight/height-^{2}[15]. The mid-arm muscle circumference (MAMC, cm), an index of the body's total skeletal muscle mass, was calculated using the equation: MAMC = MAC - (0.314±TSF)[15].

Peripheral blood was collected after overnight fasting and within 4 h of SEP test at our central laboratory using conventional methods. Serum was also measured for prealbumin and transferrin levels using a Beckman Array™ Protein System (Vigil PR$_X$™, Beckman Instruments Inc., Fullerton, California). Venous ammonia levels were tested shortly after the SEP test. Thirty-five patients had 15 min indocyanine green clearance tests within one week of SEP testing. Clinical grading of the severity of liver disease was based on Child Pugh score[16].

Peripheral blood was assayed for leukocyte subsets. One hundred μL of blood was mixed and incubated with two or three of the 20 μL fluorochrome labeled (FITC, PE or PerCP) monoclonal antibodies against T cells (CD3+, CD4 +, CD8+, IL-2R+, HLA-DR+), B cells (CD19 +), or monocytic phagocytes (CD14+, Becton Dickinson, Immuno-cytometry Systems, San Jose, California) at room temperature for 15 min. The red blood cells were lysed with 2 mL 1X FACS lysing solution for 5 min. Centrifugation, washing and dilution of the pellet were performed with PBS. Ten thousand leukocytes were measured using a FACSCAN flow cytometer for leukocytes containing fluorochrome labeled (FITC, PE, PerCP and 2,7 dichlorofluorescein) monoclonal antibodies within 6h of collection.

The study protocol was reviewed and approved under the guidelines of the 1975 Declaration of Helsinki by the Institutional Review Board of our hospital. Statistical analyses were made using the appropriate commercially available software (Microsoft Excel 97SR-1 and SPSS for Windows Release 7.0).

RESULTS

Clinical and biochemical data are shown in Table 1. All the following data are shown as mean ± standard deviation. The patients with cirrhotics with and without SPSE and the controls were sex and age matched. Cirrhotic patients had increased serum ALT levels (non- SPSE: 60 IU/L ± 76 IU/L, $P = 0.004$; SPSE: 89 IU/L ± 100 IU/L, $P = 0.001$) and total bilirubin levels (non-SPSE: 44.6 μmol/L, ± ×18.81 μmol/L, $P = 0.007$; SPSE: 64.98 μmol/L ± 106.02 μmol/ L, $P < 0.001$). Cirrhotic patients also had prolonged prothrombin time (non-SPSE: 1.9s ± 1.5s, $P = 0.001$; SPSE: 2.8s ± 1.9s, $P < 0.001$) and decreased serum albumin levels (non-SPSE: 31 g/ L ± 7 mg/ L, $P = 0.02$; SPSE: 28 g/ L ± 5g/ L, $P<0.001$). The mean venous ammonia level (non-SPSE: 29.27 μmol/ L ± 15.71 μmol/ L; SPSE: 32.84 μmol/ L ± 14.28 μmol/ L was within normal limits. None of the cirrhotic patients or control subjects had clinical PSE or abnormal venous ammonia levels. The meao percentage of the indocyanine green clearance test results was increased (non-SPSE: 27% ± 19%, $P < 0.001$; SPSE: 35% ± 17%, $P < 0.001$). Sixteen patients had indocyanine green clearance test by > 30%. Cirrhotic patients with SPSE had higher total serum bilirubin ($P = 0.03$), higher serum albumin ($P < 0.001$), and more prolonged prothrombin time ($P = 0.03$) than cirrhotic patients without SPSE.

Table 1 Vital and laboratory data of cirrhotic patients with and without SPSE

	Controls	SPSE	
	( )	(-)	(+)
	(*n* = 20)	(*n* = 27)	(*n* = 24)
Age (yrs)	53±13	57±9	59±12
Sex (M / F)	14 / 6	16 / 11	18 / 6
Total bilirubin (mg / L)	8.5±5.1	22.2±18.8[a]	64.9±106.0[bc]
Albumin (g / L)	39±7	31±7[a]	28±5[bc]
ALT (IU / L)	19±9	60±76[a]	89±100[a]
Prolonged prothrombin time (s)	0.9±0.5	1.9±1.5[a]	2.8±1.9[bc]
Indocyanine green clearance (%)	4±3	27±19[b]	35±17[bc]
Ammonia (μmol / L)	15.7±7.14	29.3±15.7	32.8±14.3
Child Pugh (A / B / C)		17 / 6 / 4	8 / 11 / 5[b]
N20-N65 inter peak latencies (ms)	40.2±3.0	45.9±8.5	50.2±9.6[bd]

[a]$P < 0.01$, compared with control subjects; [b]$P < 0.001$, compared with control subjects; [c]$P < 0.05$, compared with cirrhotic patients without SPSE, and [d]$P < 0.001$, compared with cirrhotic patients without SPSE.

Twenty-five, 17 and 9 cirrhotic patients were graded as Child-Pugh class A, B, and C, respectively (Table 2). Age, sex, serum ALT levels, venous blood ammonia levels, and N20-N65 IPLs were not different among patients in Child-Pugh classes A, B and C. Patients in Child Pugh classes B and C had lower serum albumin levels ($P < 0.001$), higher total serum bilirubin levels ($P < 0.001$), more prolonged prothrombin time ($P < 0.001$), and less clearance of indocyanine green (B *vs* A: $P < 0.05$, C *vs* A: $P < 0.001$) than patients in Child Pugh class A.

Table 2 Vital and laboratory data of cirrhotic patients in Child-Pugh classes A, B and C

	Child-Pugh		
	A	B	C
	(*n*=25)	(*n*=17)	(*n*=9)
Age (yrs)	59±9	61±6	50±11
Sex (M / F)	16 / 9	11 / 6	7 / 2
Total bilirubin (μmol / L)	15.4±6.8	27.4±12.9[a]	148.8±109.4[ab]
Albumin (g / dL)	34±5	26±3[a]	24±2[a]
ALT (IU / L)	58±56	103±59	102±83
Prolonged prothrombin time (s)	1.5±0.9	2.3±1.1[a]	4.6±1.5[ab]
Ammonia (μmol / L)	27.8±10.0	29.3±14.3	34.4±7.9
Indocyanine green clearance (%)	20±17	35±12[c]	45±9[a]
N20-N65 inter peak latencies (ms)	45.9±8.5	50.2±7.4	48.0±3.7

[a]$P < 0.001$, compared with Child-Pugh class A; [b]$P < 0.001$, compared with Child-Pugh class B; [c]$P < 0.05$, compared with Child-Pugh class A.

The mean N20 - N65 IPLs of the control subjects was 40.2±3.0 millisecond (ms); which was compatible with that of general Taiwanese population[17]. All control subjects had normal N20 - N65 IPLs. Twenty four (47.1%) cirrhotic patients had abnormal N20 - N65 IPLs. Cirrhotic patients with SPSE (50.2 ms ± 9.6 ms, $P < 0.001$) had prolonged N20 - N65 IPLs as compared with cirrhotic patients without SPSE (45.9ms ± 8.5ms) and controls. The N20 - N65 IPLs of cirrhotic patients without SPSE were not prolonged ($P < 0.001$), which were not different among patients in Child-Pugh classes A, B and C (P = NS).

Cirrhotic patients (non-SPSE: 4507/ μL ± 1546/ μL, $P<0.001$; SPSE: 4686/ μL ± 1380/ μL, $P < 0.001$) had a lower number of leukocytes than control subjects (7088/ μL ± 1557/ μL) (Table 3). The number of leukocytes were not different between the patients with and without SPSE (P = 0.06). Cirrhotic patients had lower numbers of polymorphonuclear neutrophils (non-SPSE: 2398/ μL ± 1089/ μL, $P < 0.001$; SPSE: 2714/ μL ± 1904/ μL, $P < 0.001$), and CD3+ leukocytes (non-SPSE: 586/ μL±325/ μL, $P < 0.001$; SPSE: 618/ μL ± 420/ μL, $P < 0.001$) than control subjects. The number of monocytes, eosinophils, basophils, IL-2R+ leukocytes, HLA-DR+ leukocytes, CD14+ leukocytes, and CD19 + leukocytes were not different between control subjects and cirrhotic patients. All the leukocyte subsets were not different between cirrhotic patients with and without SPSE and among the patients in Child-Pugh classes A, B and C (P = NS) (Table 4).

Table 3 Leukocyte subsets (/μL) of cirrhotic patients with and without SPSE

	Controls	SPSE	
		(-)	(+)
Leukocytes	7088±1557	4507±1546[a]	4686±1380[a]
Polymorphonuclear nutrophils	4658±1668	2398±1089[a]	2714±1904[a]
Lymphocytes	1842±747	1250±644[a]	1485±603[a]
Monocytes	376±120	305±137	307±167
Eosinophils	204±231	99±70[a]	116±88[a]
Basophils	41±28	30±15	24±24
CD3+ leukocytes	1231±557	586±325[a]	618±420[a]
CD4+ / CD8+	1.5±0.8	1.9±0.9[a]	1.9±0.9[a]
IL-2R+ leukocytes	94±61	63±58	104±106
HLA-DR+ leukocytes	30±20	76±129[a]	66±59[a]
CD14+ leukocytes	368±149	366±469	350±310
CD19+ leukocytes	218±134	199±114	169±113

[a]$P < 0.05$, compared with control subjects.

Table 4 Leukocyte subsets (/ μL) of cirrhotic patients with Child-Pugh calss A, B and C

	Child-Pugh		
	A	B	C
Leukocytes	4152±1237	3951±1097	5669±1299
Polymorphonuclear neutrophils	2306±758	2231±674	3824±1037
Lymphocytes	1418±595	1371±567	1180±422
Monocytes	280±130	245±92	442±182
Eosinophils	113±84	95±57	114±59
Basophils	31±22	29±12	38±14
CD3+ leukocytes	569±300	619±316	655±316
CD4+ / CD8+	2.0±1.0	2.0±0.7	1.7±0.6
IL-2R+ leukocytes	77±83	45±29	112±68
HLA-DR+ leukocytes	59±68	124±115	48±27
CD14+ leukocytes	326±379	327±185	510±310
CD19+ leukocytes	178±107	187±91	200±107

The data of BMI, MAMC and grip power were not different between control subjects and cirrhotic patients without and with SPSE (P = NS) (Table 5), and among patients in Child-Pugh classes A, B and C (Table 6).

Table 5 Nutritional profiles of cirrhotic patients with and without SPSE

	Controls	SPSE	
		(-)	(+)
Albumin (m / L)	39±4	31±7[a]	28±5[bc]
Prealbumin (mg / L)	313±57	125±58[d]	106±57[d]
Transferrin (mg / dL)	215±50	178±58[a]	164±46[d]
BMI (kg / m^2)	24.2±3.5	25.3±3.6	23.7±2.7
MAMC (cm)	22.1±3.6	22.7±3.5	22.2±2.6
Grip power (kg)	28.8±10.6	26.9±6.8	26.3±6.4

BMI: body mass index, MAMC: mid arm muscle circumference. [a]$P < 0.05$, compared with control subjects; [b]$P < 0.005$, compared with control subjects; [c]$P < 0.001$, compared with cirrhotic patients without SPSE; [d]$P < 0.001$, compared with control subjects.

Table 6 Nutritional profiles of cirrhotic patients in Child-Pugh classes A, B and C

	Child-Pugh		
	A	B	C
Albumin (m / L)	34±5	26±3[a]	24±2[a]
Prealbumin (mg / L)	152±52	93±31[a]	60±19[ab]
Transferrin (mg / dL)	1.96±35	1.54±39[c]	1.35±38[c]
BMI (kg / m^2)	24.3±2.6	24.9±2.5	22.9±2.1
MAMC (cm)	22.3±2.7	22.2±2.4	22.9±2.1
Grip power (kg)	30.0±8.5	27.9±6.8	22.5±6.4

BMI: body mass index, MAMC: mid arm muscle circumference. [a]$P < 0.001$, compared with Child-Pugh class A; [b]$P < 0.001$, compared with Child Pugh class B; [c]$P < 0.005$, compared with Child-Pugh class A.

The serum prealbumin and transferrin levels were lower in cirrhotic patients without (12.5 mg/ L ± 58 mg/ L, $P < 0.001$; 1.78 g/ L ± 58 g/ L, $P < 0.001$) and with (106 mg/ L ± 57 mg/ L, $P < 0.001$; 1.64 g/ L ±0.46 g/ L, $P = 0.01$) SPSE than control subjects (313 mg/ L ± 57 mg/ L and 2.15 g/ L ± 0.50 g/ L). Neither serum prealbumin ($P = 0.12$) nor transferrin ($P = 0.17$) levels were different between patients with SPSE and without SPSE. Patients in Child-Pugh class B had lower serum prealbumin and transferrin levels than patients in Child-Pugh class B ($P < 0.001$).

Based on simple linear regression, N20 - N65 IPLs of the cirrhotic patients were correlated with serum albumin levels ($r = 0.34$, $n = 51$, $P = 0.01$), but not with ammonia ($P = 0.35$), total bilirubin ($P = 0.50$), ALT ($P = 0.70$), prealbumin ($P = 0.07$), transferrin ($P = 0.88$), prothrombin time ($P = 0.26$), Child-Pugh score ($P = 0.21$), or indocyanine green clearance (P=0.80) N20-N65 IPLs did not correlated with white cell count ($P = 0.58$), leukocyte subsets ($P = 0.56$), BMI ($P = 0.20$), MCAC ($P = 0.07$), or grip power ($P = 0.79$).

DISCUSSION

PSE is one of the major complications in patients with cirrhosis. The clinical course of PSE is often unstable, and close observation is usually required to assess it. Some cirrhotic patients may have SPSE capable of disturbing daily life but without obvious impairment of mental status[14]. Psychomtric tests have been widely used for the clinical assessment of SPSE. However, poorly educated and aged subjects tend to be abnormal in psychometric tests[13,18]. Our earlier study showed that SEPs were not affected by education and age and were more sensitive than psychometric tests in the assessment of SPSE in better-educated cirrhotic patients[13]. In the present study, 24 (47.1%) of 51 cirrhotic patients developed SPSE, the data confirmed the results of our previous studies that the occurrence of SPSE was common in cirrhotic patients without clinical PSE[7,8,13].

Our data showed that cirrhotic patients in Child-Pugh classes B and C had more jaundice, lower serum albumin levels, higher serum ALT activities, more prolonged prothrombin time, and less clearance of indocyanine green than those in class A. Cirrhotic patients with poor liver function tended to develop PSE. This may explain why the occurrence of SPSE was mainly in patients in Child-Pugh class B and non-SPSE mainly in patients in class A.

Several parameters including body weight, anthropometry, and biochemical measurement are often used to assess the degree of malabsorption in cirrhotic patients[1,2,15]. In the present study, cirrhotic patients with SPSE had higher total serum bilirubin, higher serum albumin, more prolonged prothrombin time, and less clearance of indocyanine green than those without SPSE. Serum prealbumin and transferrin levels were different among cirrhotic patients in Child-Pugh classes A, B and C. Cirrhotic patients with SPSE had lower serum prealbumin and transferrin levels than patients without SPSE. Our data was compatible with the study in alcoholic cirrhosis that serum albumin, prealbumin, and transferrin levels correlated with the degree of liver damage[19]. However, our data showed that only serum albumin levels were correlated with N20 - N65 IPLs. The low albumin levels reflect the impaired hepatic synthetic functions[1,4]. The good correlation between N20 - N65 IPLs and serum albumin labels suggested that serum albumin levels are helpful in the evaluation of nutritional status in cirrhotic patients with SPSE.

It is well known that malnutrition may impair immunocompetence and increase susceptibility to infection, and leukocyte count is one of the indicators of immune status[20,21]. Peripheral blood

of cirrhotic patients had lower leukocyte count. Our data confirmed the lower leukocyte count in cirrhotic patients, and the decrease was mainly polymorphonuclear neutrophils and leukocytes. The study of leukocyte subsets further showed that the decrease of leukocytes were mainly CD3+, CD4+, and CD8+ leukocytes. The ratio of CD4+ and CD8 + was higher in cirrhotic patients compared with those of control subjects. The change of the number of leukocyte subsets was not significant among patients in Child-Pugh classes A, B and C. The number of leukocyte subsets were not different between cirrhotic patients with and without SPSE.

In this study, BMI, MAMC and grip power were not different among patients in Child-Pugh classes A, B and C; N20-N65 IPLs did not correlate with BMI, MAMC, and grip power. Our findings were compatible with recent studies[22,23] that midarm muscle area and mid-arm fat area did not relate to mortality rate of cirrhotic patients. The role of anthropometry is limited in theprediction of SPSE in cirrhotic patients.

Recent studies suggested that nutritional therapy might be helpful in the reversal of malnutrition, decreasing morbidity and nutrition, and improvement of PSE[24,25]. Thus, the early assessment of malnutrition is important. The measurement of albumin level is simple and inexpensive, and it is available to most of the clinical laboratories. It is likely that lower serum albumin levels in cirrhotic patients may suggest the possible occurrence of SPSE, and early nutritional therapy may be important to correct the malnutrition.

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