

• CLINICAL RESEARCH •

# Prevalence of subclinical hepatic encephalopathy in cirrhotic patients in China

Yu-Yuan Li, Yu-Qiang Nie, Wei-Hong Sha, Zheng Zeng, Fu-Ying Yang, Li Ping, Lin Jia

**Yu-Yuan Li, Yu-Qiang Nie, Wei-Hong Sha, Zheng Zeng, Li Ping, Lin Jia**, Department of Gastroenterology, First Municipal People's Hospital of Guangzhou 510180, Guangdong Province, China

**Fu-Ying Yang**, Department of Neurology, First Municipal People's Hospital of Guangzhou 510180, Guangdong Province, China

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**Correspondence to:** Dr. Yu-Yuan Li, Department of Gastroenterology, First Municipal People's Hospital of Guangzhou, #1 Panfu Road, Guangzhou 510180, Guangdong Province, China. liyiyi@163.net

**Telephone:** +86-20-81045208 **Fax:** +86-20-81045937

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## Abstract

**AIM:** Subclinical hepatic encephalopathy (SHE) is a common complication of liver diseases. The aim of this study was to find out the normal value of psychometric test and to investigate the prevalence of SHE in Chinese patients with stabilized hepatic cirrhosis.

**METHODS:** Four hundred and nine consecutive cirrhotic patients without overt clinical encephalopathy were screened for SHE by using number connection test part A (NCT-A) and symbol digit test (SDT). SHE was defined as presence of at least one abnormal psychometric test. The age-corrected normal values were defined as the mean $\pm$ 2 times standard deviation (2SD), and developed in 356 healthy persons as normal controls. Four hundred and sixteen patients with chronic viral hepatitis were tested as negative controls to assess the diagnostic validity of this test battery.

**RESULTS:** There was no significant difference in NCT scores and SDT quotients between healthy controls and chronic hepatitis group ( $P>0.05$ ). In all age subgroups, the NCT and SDT measurements of cirrhotic patients differed significantly from those of the controls ( $P<0.05$ ). When mean $\pm$ 2SD of SDT and NCT measurements from healthy control group was set as the normal range, 119 cirrhotic patients (29.1%) were found to have abnormal NCT-A and SDT tests, 53 (13.0%) were abnormal only in SDT and 36 (8.8%) only in NCT-A. Taken together, SHE was diagnosed in 208 (50.9%) cirrhotic patients by this test battery. The prevalence of SHE increased from 39.9% and 55.2% in Child-Pugh's grade A and B groups to 71.8% in Child-Pugh's grade C group ( $P<0.05$ ). After the adjustment of age and residential areas required from the tests, no correlation was found in the rate of SHE and causes of cirrhosis, education level and smoking habit.

**CONCLUSION:** Psychometric tests are simple and reliable indicators for screening SHE among Chinese cirrhotic patients. By using a NCT and SDT battery, SHE could be found in 50.9% of cirrhotic patients without overt clinical encephalopathy. The prevalence of SHE is significantly correlated with the severity of liver functions.

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## INTRODUCTION

Subclinical hepatic encephalopathy (SHE) has been defined as a condition in which patients with cirrhosis regardless of its etiology, demonstrates neuro-psychiatric and neuro-physiological defects, yet, having a normal mental and neurological status through global clinical examination<sup>[1-3]</sup>. SHE could have some disadvantageous influence on patients' daily life, and could be a preceding stage of manifested hepatic encephalopathy (HE) clinically. The prevalence of SHE was reported to vary from 10% to 84%, depending on the diagnostic techniques used and patients selected for the studies<sup>[1-10]</sup>. Many diagnostic techniques including psychometric test, electro-encephalogram, evoked potentials (EP), have been used to detect SHE. Among these tests, only psychometric test can be administered easily in epidemiological studies. In a variety of psychometric tests listed in the medical literature, SDT and NCT part A (NCT-A) were reported to have the advantages of simplicity and reliability<sup>[1,11-15]</sup>. The combination of these two tests was commonly applied in epidemiological studies. We evaluated a battery of SDT and NCT tests in a pilot study in Chinese patients with good results<sup>[16]</sup>. Therefore, it was selected in this big sample size study. By definition, SHE can only be found in cirrhotic patients. In this study, besides the healthy control group for the establishment of normal values of SDT and NCT, we also set up a chronic hepatitis group as negative control to assess the reliability of SDT and NCT test battery. In recent years, studies on the prevalence of SHE have been greatly increased in Western literature, but those from Chinese patients have not been fully documented. The aim of the present study was to establish the normal value of psychometric tests for Chinese people, to determine the prevalence of SHE in stable cirrhotic patients in China by using this test battery, and to explore the features of SHE in these patients.

## MATERIALS AND METHODS

### Subjects

Four hundred and nine consecutive cirrhotic patients attending the Department of Gastroenterology of Guangzhou Municipal First People's Hospital for screening of SHE from June 1, 1998 to March 31, 2002 were included in the study. Inclusion criteria were: no neurological or mental diseases, no attack of HE in the past or present, no use of sedative or other psychotropic drugs two wk prior to the tests. The following patients were excluded. Those who had portosystemic shunt operation, those who had alcohol consuming more than 150 g daily within 1 wk prior to the study, those who had gastrointestinal bleeding 4 wk previously, those whose hemoglobin level was less than 90 g/L, those who had dehydration or electrolyte imbalance, those whose body temperature was higher than 37.5 °C, those who had severe cardiac or pulmonary or renal or cerebrovascular

diseases or diabetes mellitus, and those who were illiterates.

Diagnosis of cirrhosis was made according to the criteria revised in 1990 National Symposium on Cirrhosis in China<sup>[17]</sup>. In this study, 10 patients had liver biopsy. The Child-Pugh's scores were used to assess the severity of liver disease. Special attention was paid to the exclusion of stage 1 HE. The symptoms in this stage included abnormal behavior (exaggeration of normal behavior, euphoria or depression), sleeping disorders (hypersomnia, insomnia or inversion of sleeping pattern), neuromuscular activity (muscular incoordination, impaired handwriting) and changes in mental function (declined alertness or memory, subtle disorientation or impaired calculation). The etiology of the 409 cirrhotic patients consisted of chronic hepatitis B in 322 (78.7%), chronic hepatitis C in 28 (6.9%), and chronic alcoholics in 59 (14.4%). According to the Child-Pugh's grading of liver function, 188 (46.0%) were grade A, 143 (35.0%) grade B and 78 (19.0%) grade C. Two hundred and fourteen patients (52.3%) had no ascites, 72 (17.6%) had mild ascities and 123 (30.1%) had severe ascities. One hundred and sixty-nine patients (41.3%) had normal levels of serum albumin, 102 (24.9%) had mild hypoalbuminemia (30-35 g/L) and 138 (38.8%) had severe hypoalbuminemia (<30 g/L). One hundred and twenty-three patients (30.1%) had normal prothrombin time (PT), 152 (37.2%) had mildly prolonged PT (14-18 s) and 134 (32.7%) severely prolonged PT (>18 seconds). Under endoscopic examination, 28 patients (6.8%) had severe esophageal varices, 152 (37.2%) had mild varices and 229 (56.0%) had no varices.

Normal values of the psychometric tests were obtained from 356 consecutive healthy subjects undergoing routine physical check-up in the hospital between June 1 and July 1, 1998. All of them had no physical and psychological disorders, no neurological or mental diseases and no history of sedatives or alcohol consumption. The negative control group consisted of 416 consecutive outpatients with chronic viral hepatitis in Division of Infectious Diseases of our hospital in the same period. The diagnostic criteria were in accordance with the Chinese National Standards of Viral Hepatitis<sup>[18]</sup>. Among the 416 cases, 384 (92.3%) had hepatitis B, 32 (7.7%) hepatitis C.

The study was approved by the Ethics Committee of the First Municipal People's Hospital of Guangzhou, Guangzhou Medical College, with written consent from each patient and subject.

### Questionnaire

Questionnaire was given to each subject. It included the following items, namely age, sex, smoking habit (smoking cigarette daily, yes/no), alcohol (drinking alcohol daily, yes/no), education (<6 years, 6-12 years, >12 years), residential area (urban/rural), occupation, history of liver diseases, concomitant illness.

### Psychometric assessment

Symbol digit test (SDT) was in Chinese version of Wechsler adult intelligence scale revised (WAIS-RC) by Gong<sup>[19]</sup>. The individuals were given a list of digits from 1 to 9 associated with symbols and asked to fill in blanks with symbols that corresponded to each number. An initial demonstration was performed to familiarize the subjects with the test. The test scores were the total number of correctly sequential matched symbols to the number within a 90-seconds interval. The score was only 0.5, if the symbol was placed upside down. According to age, the total score of each subject was transformed to a quotient from an equivalent form, the subjects were divided into two groups according to their residential areas, either rural or urban area.

In the number connection test (NCT) part A, the subjects were asked to connect the numbers printed on the paper

consecutively from 1 to 25 as quickly as possible<sup>[20]</sup>. After explanation to the subjects, demonstrative tests were given to ensure a correct understanding and then the test was carried on. The test scores included the time required for the test and for correcting the errors.

These two psychometric tests were performed by the patients and subjects with help from medical staffs without awareness of the diagnosis.

### Statistical analysis

Student's *t* test and Chi-square test were used to assess the differences among the groups. Multivariate logistic analysis was used to evaluate the influence of the variables in the prevalence.  $P < 0.05$  was considered statistically significant. Normal cut-off values of SDT and NCT were set at the mean  $\pm$  2SD from the normal control arm, with a low value indicating a poor performance in SDT test and a higher score indicating a poor performance in NCT test. The diagnosis of SHE was made when one or both SDT and NCT appeared abnormal.

## RESULTS

The demographic data of three arms are shown in Table 1. There was no significant difference ( $P > 0.05$ ) among all variables from the three arms. The results of SDT and NCT in different age subgroups from the three arms are shown in Table 2 and Table 3. In both tests, no significant difference was found between healthy controls and chronic hepatitis arms ( $P > 0.05$ ). However, the results in the cirrhotic arm differed significantly from those of the two control arms ( $P < 0.05$ ). This finding supported that the Chinese version of SDT and NCT tests could clearly distinguish the neuro-psychiatric defects in SHE. The values of SDT and NCT tests from the healthy control arm could be good parameters for the establishment of normal values of these two tests.

**Table 1** Demography in 3 groups

	Control <i>n</i> = 356	Hepatitis <i>n</i> = 416	Cirrhosis <i>n</i> = 409
Age (yr)	44.4 $\pm$ 12.7	36.8 $\pm$ 18.6	53.4 $\pm$ 11.9
Male/female	207/149	330/86	248/161
Education (yr)			
>6	69 (19.4)	69 (16.9)	82 (20.0)
6-12	168 (47.2)	215 (51.7)	190 (46.5)
> 12	119 (33.4)	132 (31.7)	137 (33.5)
Smoking	65 (18.3)	99 (23.8)	88 (21.5)
Alcohol	39 (10.9)	48 (11.5)	123 (30.1)

The influence of the variables on the results of SDT and NCT is shown in Table 4. No significant difference was found in sex, smoking and alcohol drinking habits, and the etiology of cirrhosis ( $P > 0.05$ ), but the difference was related to age, education and Child-Pugh's grade ( $P < 0.05$ ). However, after adjustment of age and residential areas required for SDT and NCT tests, Child-Pugh's grade was the only risk factor of SHE ( $P < 0.05$ ).

The relationships between Child-Pugh's grade and SDT/NCT are shown in Table 5. Although the rate of SHE between Child's grades A and B of liver disease was not significantly different ( $P > 0.05$ ), significance was found between grades A and C, and grades B and C ( $P < 0.05$ ). One hundred and nineteen patients (29.1%) were abnormal in both NCT and SDT, 53 (13.0%) abnormal in SDT only and 36 (8.8%) in NCT-A only. Taken together, the two-test battery gave the diagnostic rate of SHE in 50.9% of 208 patients.

**Table 2** Results of SDT in 3 groups

Age (yr)	Control		Hepatitis		Cirrhosis	
	<i>n</i>	mean±SD	<i>n</i>	mean±SD	<i>n</i>	mean±SD
</=34	82	12.5±2.2	176	12.7±3.1	52	10.8±2.8 <sup>a</sup>
35-44	76	11.9±1.7	114	12.3±3.5	73	9.4±2.7 <sup>a</sup>
45-54	74	12.8±2.3	71	12.3±2.2	107	8.9±2.5 <sup>a</sup>
55-64	69	11.9±2.1	35	11.5±1.6	87	7.8±2.5 <sup>a</sup>
>/=65	54	12.7±2.4	20	9.0±2.2	90	6.7±2.3 <sup>a</sup>
Total	356	12.2±2.3	416	12.2±3.1	409	8.5±2.8 <sup>a</sup>

<sup>a</sup>*P*<0.05 vs normal control and chronic hepatitis.**Table 3** Results of NCT in 3 groups

Age (yr)	Control		Hepatitis		Cirrhosis <sup>a</sup>	
	<i>n</i>	mean±SD	<i>n</i>	mean±SD	<i>n</i>	mean±SD
</=34	82	26.7±8.8	176	27.0±6.9	52	46.1±19.2
35-44	76	34.2±12.7	114	35.8±20.3	73	51.4±26.5
45-54	74	39.8±13.8	71	41.9±12.7	107	59.3±30.8
55-64	69	52.7±13.5	35	54.3±7.3	87	71.1±41.8
>/=65	55	69.9±14.8	20	80.1±12.1	90	102.3±48.8
Total	356	47.8±13.2	416	36.8±18.6	409	68.2±41.2

<sup>a</sup>*P*<0.05 vs cirrhosis versus normal control and chronic hepatitis.**Table 4** Multivariate logistic analysis for risk factors in cirrhotic group

	<i>n</i>	NCT	DST	SHE(%)	p2	OR
Sex					0.494	0.9
Male	344	67.4±42.1	8.6±2.8	51.2		
Female	65	72.4±36.0	8.7±2.6	52.3		
p1		0.367	0.266	0.866		
Smoking					0.903	1.0
Yes	288	6.2±38.7	8.6±2.6	51.0		
No	121	672.8±46.4	8.3±2.9	52.1		
p1		0.145	0.358	0.850		
Etiology					0.430	0.8
Alcohol	59	71.3±40.1	8.0±2.6	54.2		
Non-alcohol	350	67.7±41.4	8.6±2.9	51.0		
p1		0.541	0.153	0.646		
Education (yr)					0.390	0.9
< 6	72	92.8±50.0	6.9±2.4	51.4		
6-12	199	69.6±41.1	8.2±2.6	55.3		
> 12	138	53.3±27.6	9.7±2.9	45.3		
p1		0.001	0.001	0.221		
Age (yr)					0.779	1.0
< 35	52	46.1±19.2	10.8±2.8	51.9		
35-44	73	51.4±26.5	9.4±2.7	52.1		
45-54	107	59.3±30.8	8.9±2.5	49.5		
55-64	87	71.1±41.8	7.8±2.5	50.0		
> 65	90	102.3±48.8	6.7±2.3	57.8		
p1		0.001	0.001	0.617		
Child-Pugh					0.001	2.0
A	188	58.5±34.9	9.3±2.8	39.9%		
B	143	72.8±41.2	8.1±2.8	55.2%		
C	78	83.1±49.1	7.4±2.6	71.8%		
p1		0.001	0.001	0.001		

p1: *P* value within groups. p2: *P* value among groups in logistic analysis.

**Table 5** Relationships between psychometric tests and Child-Pugh's grade

	Child's A	Child's B	Child's C	Total (n,%)
<i>n</i>	188	143	78	409
Abnormal in SDT	23	20	10	53 (13.0)
Abnormal in NCT	16	10	10	36 (8.8)
Abnormal in SDT and NCT	35	48	36	119 (29.1)
Total (%)	74 (39.4)	78 (54.5)	56 (71.9) <sup>a</sup>	208 (50.9)

<sup>a</sup>*P* < 0.05.

## DISCUSSION

The reasons why we selected SDT and NCT part A out of a variety of psychometric tests from the medical literature in this study are as follows. (1) NCT and SDT were simple, inexpensive and sensitive tests and have been well used in many SHE studies on its prevalence, prognosis and treatment<sup>[1-15]</sup>. NCT part A alone has been shown to be sufficient in detection of SHE in the majority of patients<sup>[3,12]</sup>. (2) The patients with SHE exhibited selective deficits in reactivity and fine motor skills, with preservation of general intelligence, memory and language speaking. Therefore, it was reasonable to select WAIS performance subtests such as SDT<sup>[11,12]</sup>. (3) Both SDT and NCT were easy to perform and reproduce in minutes at the outpatient clinics. Moreover more complicated tests would increase the patients' fatigue and mental burden and affect their performance efficiency<sup>[11]</sup>. In order to evaluate the reliability of SDT/NCT test battery, two control groups were set up. Normal data of each age subgroup in the two tests were obtained from healthy subjects and then assessed with the data from chronic hepatitis negative control and cirrhosis positive control. The corresponding scores of the tests from healthy and chronic hepatitis control groups were very close. By using the normal range drawn from healthy subjects, the total abnormal rate of SDT and NCT in chronic hepatitis group was 5.5% and 7.2% respectively, near marginally statistical range. The results supported that SDT and NCT test battery was a sensitive and specific method for detection of SHE.

Whether or not the patients with alcoholic cirrhosis have a higher prevalence of SHE is still controversial. The higher prevalence of SHE in patients with alcoholic cirrhosis was mostly reported from the studies using EP or electroencephalogram<sup>[21]</sup>, suggesting a diffuse neurological disturbance in alcoholic cirrhotic patients. In China, most cirrhotic patients were caused by chronic hepatitis B. No significant difference in various etiologies was found among the subgroups in this investigation, probably due to the application of psychometric measures only. Some reports supposed that the elder and educational levels might influence the results of psychometric tests<sup>[22,23]</sup>. No significant correlation was found between the different subgroups in age and education in the present study, since we used age-related normal values to correct the findings.

The selected subjects in this study reflected the real spectrum of cirrhotic patients in Guangzhou. The detected SHE prevalence was 50.9%, with its rate increased from 39.4% in Child-Pugh's grade A to 54.5% and 71.9% in grades B and C. These results agreed well with the data reported from Western literature. The patients with worse liver functions assessed by Child-Pugh's grade had a higher rate of SHE. Child-Pugh's scores were based on patients' symptoms (HE and ascites) and laboratory tests (serum levels of albumin, bilirubin, prothrombin). Patients with HE were excluded from this study. We also observed that the patients who had more or severer symptoms and poorer laboratory parameters of cirrhosis whether or not including in Child-Pugh's grade might tend to develop SHE.

Patients with SHE appeared to have no clinical symptoms. However, they might be at risk when they performed complex

motor activities as operating a heavy machinery or driving an automobile<sup>[24]</sup>. They might have abnormal behaviors such as altered sleeping pattern and impaired cognitive function<sup>[25,26]</sup>. Patients with SHE were vulnerable to HE<sup>[27-29]</sup>. However, medical treatment and dietary management in these patients could improve the psychometric tests<sup>[28-30]</sup>. Early diagnosis and treatment of SHE seem extremely important in China, because of the big population and high prevalence of liver diseases in this country. A high prevalence of SHE in cirrhotic patients should lead us to pay attention to these important findings frequently encountered in our medical practice.

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