The Diagnosis of Subclinical Hepatic Encephalopathy in Patients With Cirrhosis Using Neuropsychological Tests and Automated Electroencephalogram Analysis

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Neuropsychological tests used for the assessment of subclinical hepatic encephalopathy (SHE) may overdiagnose SHE because scores are usually not corrected for age. The aim of this study was to estimate the prevalence of SHE using two easy administrable psychometric tests (Number Connection Test part A [NCT-A], Symbol Digit Test [SDT]) with age-related normal values. In addition, spectral electroencephalogram (EEG) was used, which is the in-house electrophysiological method for quantifying encephalopathy.

One hundred and thirty-seven consecutive patients (mean age 49 years, range 17-77) with cirrhosis without any clinical signs of encephalopathy, were screened for SHE. In addition, the Child-Pugh score and the arterial blood ammonia were determined. Patients with concurrent use of alcohol, benzodiazepines or anti-epileptics were excluded.

Fifty percent of the patients had an abnormal NCT according to the standard recommended procedure, in contrast only 7% of the patients had an abnormal NCT when scores corrected for age were used. Combining the results of the spectral EEG and the psychometric tests corrected for age yielded a higher prevalence of SHE (23%) than when each test method was used alone (17% vs. 10% abnormal, respectively). Severity of liver disease correlated with the presence of SHE, because the prevalence of abnormal tests increased from 14% in Child-Pugh grade A to 45% in Child-Pugh grade B or C. Age above 40 years and an elevated blood ammonia level were significant determinants related to an abnormal EEG. We conclude that the NCT uncorrected for age markedly overdiagnoses SHE and, therefore, should not be used as a test for the screening of SHE. Using a combination of spectral EEG and two psychometric tests with age-corrected normal values a low prevalence of SHE in patients with Child A liver cirrhosis is found. Older patients with an elevated arterial ammonia are more prone to develop SHE than younger patients with an equal arterial ammonia concentration. (HEPATOLOGY 1996;24:556-560.)

Abbreviations: HE, hepatic encephalopathy; SHE, subclinical hepatic encephalopathy; NCT, Number Connection Test; EEG, electroencephalogram.

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Received July 18, 1995; accepted April 27, 1996.

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0270-9139/96/2403-0016$3.00/0

Hepatic encephalopathy (HE) is a serious complication of advanced liver disease and refers to neuropsychiatric abnormalities (such as disorders of personality, altered levels of consciousness, impairment of intellectual function), and neuromuscular dysfunction (asterixis) because of liver insufficiency.[1] Traditionally HE is graded into four clinical stages of severity, ranging from abnormal behavior to coma.[2] In addition to the clinical grading of HE, a subclinical stage has been described, in which patients with cirrhosis, regardless of its cause, show a number of quantifiable neuropsychological defects, yet have a normal mental and neurological status on global clinical examination.[3-13] The prevalence of this subclinical hepatic encephalopathy (SHE) has been reported to vary from 30%[13] to 84%,[11] depending on the tests and population used.

The neuropsychological defects found in SHE may have a negative effect on patients' daily life.[6,14] In addition, these defects are considered to be a preclinical stage of clinical manifest HE.[4,9,15] In view of the reported high incidence of SHE in patients with cirrhosis and its possible impact on daily life, routine assessment of early stages of HE is recommended,[4,6,9,16] as this syndrome may be fully reversible with treatment.[4,17-20] However, the extensive neuropsychological test batteries used in most studies (up to 21 different psychometric tests![9]), are not suitable for a fast routine screening in an outpatient clinic. Conn[21] suggested to use the Number Connection Test (NCT) as a sole psychometric test for quantifying HE. Other investigators[4,9,12,13,22] have proposed to use a combination of two to three psychometric tests as a diagnostic screen for SHE. As neuropsychological performance is known to be influenced by age,[23,24] education,[24] and repetitive testing,[21] several investigators have used neurophysiological tools such as evoked potentials[15,25,26] or quantitative electroencephalogram (EEG) analysis[27] for the diagnosis of SHE. However, controversy exists in literature whether these neurophysiological methods are as sensitive as psychometric tests.[28,29]

The aim of the present study was to determine the prevalence of neuropsychological and neurophysiological defects in stable cirrhotic patients attending a university hospital outpatient clinic. Two psychometric tests with age-corrected normal values (NCT part A,[30] Symbol Digit Test[31]) were selected to be used as a neuropsychological screen. These two tests are easy to administer, have a reported high sensitivity in detecting SHE,[3-5,8,9,12,13] and can be performed within 5 minutes at the outpatient clinic. Spectral analysis of the EEG, which is the standard in-house electrophysiological method for grading HE,[27] was used as a screen for neurophysiological defects. In addition, the arterial ammonia concentration was determined in each patient to assess whether the defects found at screening could be considered because of liver insufficiency and/or portosystemic shunting; the Child-Pugh score was determined to assess the severity of the chronic liver disease.

TABLE 1. Prevalence of Abnormal Psychometric Tests and Abnormal Spectral EEG in 137 Cirrhotic Patients Without Clinical Hepatic Encephalopathy

Diagnostic Test	No. Tested	No. Abnormal	% Abnormal
NCT-A (corrected for age)	137	9	7
Symbol digit test	136	7	5
≥1 Abnormal psychometric test	137	14	10
Spectral EEG	137	23	17

PATIENTS AND METHODS

Subjects

From January 1, 1992 to December 31, 1993, 137 consecutive biopsy-proven cirrhotic patients (99 male, 38 female, mean age 49 years, SD 14, range 17-77) without any clinical signs of HE attending the outpatient clinic of Internal Medicine II and Hepatogastroenterology of the University Hospital Rotterdam-Dijkzigt were screened for SHE. The cause of the cirrhosis was chronic viral hepatitis in 62 patients, alcohol abuse in 31 patients, and other causes (e.g., autoimmune, primary biliary cirrhosis, cryptogenic) in 44 patients. Patients diagnosed by the investigators or their treating physician as active alcohol abusers (excessive alcohol intake in the preceding 6 weeks, or deterioration of the blood transaminase levels in the preceding outpatient control visits) and patients using benzodiazepines or anti-epileptics were excluded.

None of the patients had evidence of neurological and/or psychiatric abnormalities on global clinical examination performed in each patient by the same examiner (J.C.Q.). Mental state assessment included state of awareness; "Is the patient perfectly alert and well oriented in time, place, and person?". The level of attention (primary memory) and concentration was assessed by asking the patient to subtract serial sevens from 100 and to repeat a series of six nonconsecutive numbers in the same order (a normal individual can easily remember seven numbers forwards). Secondary memory (recent memory, new learning, encoding) was tested by asking the patient to remember three objects and to repeat these several minutes later. Remote memory (ability to recall events of weeks or years ago) was assessed by asking the patient about past presidents, dates of wars, and events that affect everyone.

Neuropsychological Assesment

Number Connection Test. This test is a derivative from the Trail Making Test[32] and measures cognitive motor abilities. In the NCT, subjects have to connect numbers printed on paper consecutively from 1 to 25, as quickly as possible. Errors are not enumerated, but patients are instructed to return to the preceding correct number and then carry on. The test score is the time the patient needs to perform the test, including the time needed to correct the errors. A low score indicates a good performance. Age dependent normal values of this NCT[30] have been developed in 681 persons without liver disease.[33] Normal values are expressed as the mean ± 2 standard deviations.

Symbol Digit Test. This is a subtest of the Wechsler Adult Intelligence Scale (WAIS) and measures motor speed and accuracy.[31] The patient is given a list of symbols associated with digits from 1 to 9 and is asked to fill in blanks with numbers that correspond to each symbol. The test score is the total number of correct sequential matchings of numbers to symbols in a 90-second interval. A high score indicates a good performance. Data of 2,169 Dutch and Belgian persons serve as a reference group in the Netherlands.[34] These normative data are expressed in percentiles. We considered a test result below the 2.5th percentile (i.e., approximately the mean minus 2 standard deviations) as abnormal.

After explanation of each psychometric test, an abbreviated demonstration test was administered to ensure that the patient understood the test correctly. In addition, the patient could adapt to the most convenient sitting position after the demonstration test. Attention was paid to the lighting of the room, and whether the patient was wearing his reading glasses. Patients likely to have difficulties performing the psychometric tests, such as those with neurological diseases or bad vision, were excluded from this study.

Neurophysiological Assessment

The EEG was recorded using standardized techniques (Nihon Kohden) while the patient, with the eyes closed, laid comfortably in a quiet room. When drowsiness occurred an auditory stimulus was applied by the EEG technician. Four electrodes were attached to the skin at the positions T3, T4, O1, and O2 according to the international "10-20 system."[35] Electrode impedance was kept lower than 5 kΩ. After applying the usual bandpass filters (0.53 - 35 Hz) two runs of 100 seconds each were recorded and compared for reproducibility. Artefact free recordings were selected and fed into a computer after analogue-digital conversion (sample frequency 102.4 Hz). Ten epochs of 10 seconds each were analyzed by applying Fast Fourier Transformation and the mean power spectrum calculated. Patients are graded in the different stages of HE on account of their mean dominant frequency, and the relative powers of δ and θ activity. In a previous study[27] we have validated this method in 51 healthy controls (median age 41 years, range 21-78) and 66 patients with cirrhosis of the liver (median age 60 years, range 12-75). A θ activity above the 97.5th percentile (i.e., approximately the mean plus two standard deviations) in controls (i.e., >35% θ activity) was considered abnormal.

Laboratory Assessments

The Child-Pugh score was used to assess the severity of liver disease.[36] Three biochemical variables (serum albumin, bilirubin, and prothrombin time) and two clinical characteristics (presence or absence of ascites and encephalopathy) determine the Child-Pugh score. Each variable is given 1 to 3 points, leading to scores ranging from 5 (excellent liver function) to 15 points (poor liver function). In addition, arterial ammonia levels were measured, using the Dupont aca procedure (Dimension SMS) (Dupont de Nemours; Wilmington, DE)[37] or the Blood Ammonia Checker II (Kyoto Daiichi; Kyoto, Japan).[38]

Statistical Analysis

Kappa was used as a measure of agreement of various tests. Wilcoxon's rank sum test or the Fisher Exact test were used to assess differences in clinical and laboratory characteristics of patient groups. Those variables reaching statistical significance in the univariate analysis, when clinical and laboratory data were compared between normal and at least one abnormal psychometric test, were selected for multivariate analysis using multiple logistic regression.[39] The same procedure was performed for EEG abnormality. The limit for statistical significance was set at $P = .05$.

RESULTS

None of the stable cirrhotic patients included in the study had clinical signs of hepatic encephalopathy. A good liver function, which was defined as Child-Pugh grade A, was present in 71% of the patients.

Fifty percent of the patients had an NCT score of more than 30 seconds, which is considered abnormal according to the Portal Systemic Encephalopathy index (PSE-index).[40]

TABLE 2. Relation Between Psychometric Tests and Spectral EEG in 137 Cirrhotic Patients Without Clinical Signs of Hepatic Encephalopathy

	Spectral EEG		
	Normal	Abnormal	
*NCT			
Normal	107	21	128
Abnormal	7	2	9
	114	23	137
†SDT			
Normal	111	19	130
Abnormal	3	4	14
	114	23	137
‡NCT and SDT normal	105	18	123
†NCT or SDT abnormal	9	5	14
	114	23	137

* Observed agreement: (107 +2)/137 = 0.80 κ: .03.

† Observed agreement: (111 +4)/137 = 0.84 κ: .20.

‡ Observed agreement: (105 + 5)/137 = 0.80 κ: .16.

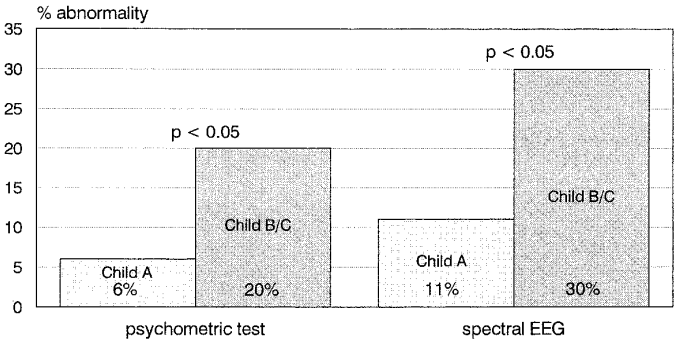

FIG. 1. Percentage of abnormal test results in cirrhotic patients with a good liver function (Child-Pugh grade A, n = 97) and cirrhotic patients with a diminished liver function (Child-Pugh grade B or C, n = 40) ▭, Child A (n = 97); ▭, Child B/C (n = 40).

TABLE 4. Multivariate Analysis of the Probability of Abnormal Test Results

		Abnormal Spectral EEG		Abnormal Psychometric Test	
		Odds-Ratio	*P*	Odds-Ratio	*P*
Age		1.8*	.01	1.8*	.04
Ammonia		3.1†	.01	1.2†	.74
Child-Pugh	A‡	1	—	1	—
	B/C	1.1	.94	2.4	.26
Alcoholic	No‡	1	—	1	—
	Yes	1.7	.36	1.6	.48

NOTE. Odds-ratios are given for an abnormal EEG and for at least one abnormal psychometric test (odd-ratios of 1 indicate no association).

* As compared with 10 years younger.

† As compared with a 50% lower NH_3.

‡ Reference category.

However, the patients' age is not taken into account in this test, which is reflected by the fact that when age dependent normal values were used, only 7% of the patients scored abnormal. Table 1 summarizes the prevalence of abnormality in age-corrected psychometric tests and spectral EEG found in our population.

The agreement between the outcomes of the psychometric tests and spectral EEG was poor ($\kappa = 0.16$). Only 16% (5/32) of the patients scored abnormal on both tests (Table 2).

When patients were classified according to the severity of their liver disease, the percentage abnormality in psychometric tests increased from 6% in Child-Pugh grade A to 20% in Child-Pugh grade B or C. A 2- to 3-fold increase in abnormality in patients with a diminished liver function was also seen in the spectral EEG (Fig. 1). Both findings were statistically significant ($P = .03$ and .01, respectively, Fisher Exact test).

Clinical and laboratory characteristics of patients with abnormal psychometric tests and abnormal spectral EEG are summarized in Table 3. Males and females were equally distributed among the groups with normal and abnormal test results.

In patients with alcoholic cirrhosis, a higher prevalence of abnormal tests was found compared with patients with nonalcoholic cirrhosis. Especially, the spectral EEG was more disturbed in the alcoholic group. A probable confounder in this finding was the severity of liver disease, as a Child-Pugh grade of B or C was more frequently found in alcohol-induced cirrhosis than in nonalcohol-induced (48% vs. 24%, respectively, $P < .01$). Therefore, multivariate analysis of the factors found to be significantly different between patients with normal or abnormal test outcomes in the univariate analysis (age, ammonia, Child-Pugh class, and alcoholic origin) was performed. Age remained the only significant factor related to abnormality in psychometric tests (Table 4). However, related to an abnormal EEG, the arterial ammonia concentration in addition to age was found to be a significant determinant (Table 4). Having patients grouped to age, Fig. 2 shows the probability of having an abnormal EEG according to both age and ammonia concentration arising from multiple logistic regression (Table 4).

TABLE 3. Clinical and Laboratory Characteristics of the Cirrhotic Patients With Normal and Abnormal Psychometric Tests (3A) and Spectral-EEG (3B)

	Normal NCT and SDT	Abnormal NCT or SDT	*P*
3A			
Patient number	123	14	
♂♂:♀♀	88:35	11:3	.8
Age (y)	48.1 ± 14	58.1 ± 11	<.05
Arterial NH_3 (μmol/L)	54.3 ± 33	70.2 ± 30	.12
Child-Pugh B or C	26%	47%	<.05
Alcohol as cause	21%	36%	.31
	Normal EEG	**Abnormal EEG**	**P**
3B			
Patient number	114	23	
♂♂:♀♀	81:33	18:5	.6
Age (y)	47.2 ± 14	58.5 ± 11	<.01
Arterial NH_3 (μmol/L)	51.4 ± 32	75.1 ± 26	<.001
Child-Pugh B or C	25%	52%	<.05
Alcohol as cause	19%	39%	<.05

DISCUSSION

According to literature, SHE is present in 30% to 84% of the patients with cirrhosis.[13,11] Many physicians of our Hepatogastroenterology department doubt this reported high prevalence, because in their clinical experience most cirrhotic patients are normal at clinical examination and do not complain about diminished memory or concentration. Therefore, we performed a study to determine the prevalence of SHE in our patient population with cirrhosis.

Our results confirm the presence of abnormal neuropsychological and/or neurophysiological abnormalities in patients with stable cirrhosis, however the prevalence found by us was lower than that reported in literature.[4,9,11,12] We found that 10% of our cirrhotic patients scored abnormal in at least one out of two psychometric tests and that 17% had an abnormal spectral EEG. Using the established definition of SHE

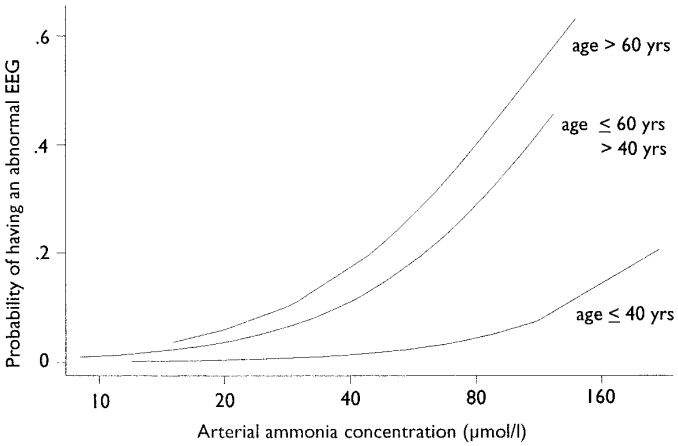

FIG. 2. Probability of having an abnormal spectral EEG in different patient age groups according to the arterial ammonia concentration. (Note: logarithmically transformed horizontal axis).

(i.e., neuropsychological and/or neurophysiological defects in patients with no signs of HE on clinical examination) 23% of our cirrhotic patients had SHE.

We believe our findings to be reliable, because the study including both neuropsychological and neurophysiological methods was performed in a large patient size. Furthermore, to avoid interobserver variability all patients were clinically and neuropsychologically assessed by the same examiner. In addition, spectral EEG analysis was used, which is the most objective method for EEG grading. Lastly, one of the most important conditions in selecting psychometric tests we fulfilled was the use of normal values corrected for age.[23,24] Our results show the effect of age on neuropsychological performance; 50% of our patients had an abnormal standard NCT,[40] but only 7% were abnormal when age-corrected scores were used. Our results are in agreement with those of Koch et al.,[22] who used exactly the same NCT forms and age-corrected scores[30] as in our study.

With regard to spectral EEG as well as age-corrected NCT, our results confirm those of Weissenborn et al.,[26] who performed a similar study in a much smaller study population (n = 29).

Were the diagnostic methods used by us sensitive enough to detect SHE? We selected the NCT part A and SDT out of a large variety (approximately 70!) of psychometric tests used in literature,[41] because these two tests are reported to be sensitive, and can be administered easily during a routine control visit of a cirrhotic patient to a hepatology outpatient clinic. The NCT part B, in which patients have to connect numbers and letters in consecutive order, has been reported to be more sensitive than the NCT part A, because this test has an increased attentional load.[26] Therefore, exclusion of the NCT part B could have lowered our diagnostic sensitivity. However, this test could not be performed in all our patients, because part of our patient population consists of foreign laborers, who are not familiar with the English alphabet. To document this, we administered the NCT part B test in a subpopulation of 83 cirrhotic patients. Seven out of 19 foreign patients were not able to perform this test because of insufficient knowledge of the English alphabet. Of the remaining 76 patients, 18% scored abnormal in the NCT part B test. However, this result must be interpreted with caution because 33% of the Dutch speaking foreigners scored abnormal in the NCT part B test in contrast to 11% of the native Dutch patients (data not shown). The percentage of abnormality in the NCT part B test results probably would have been lower if we had also excluded patients with less than 8 years of education.[24] We therefore selected only neuropsychological tests, the performance of which was hardly influenced by education and cultural background.

The number of diagnostic tests, the definition of SHE, and the patient population studied probably had their implications for the prevalence of SHE found. We found a SHE prevalence of 23%, defining SHE as at least one abnormal test out of two psychometric tests or an abnormal spectral EEG. Gitlin et al.[9] found a prevalence of 70%, when SHE was defined as at least two abnormal tests out of 21. In addition, the definition of abnormal (values less than the 2.5th, 5th, or 10th percentile from a control group) could explain the wide range of SHE prevalence found in the various studies.

The prevalence of SHE will also vary depending on the population tested. Our patient population consisted mainly of stable cirrhotic patients with a good liver function, which could explain the low prevalence of SHE found by us. Although controversy exists in literature, whether liver function correlates with SHE,[5,6,22,29,42,43] we found a significant increase in the prevalence of SHE from 14% (CI 7-21) in Child-Pugh grade A to 45% (CI 28-61) in Child-Pugh grade B or C. Another finding in our study was the poor overlap between abnormal psychometric tests and spectral EEG. It was not the intention of the study to determine whether psychometric tests are more sensitive than electrophysiological tests in diagnosing SHE. This question cannot be answered from our results because we used prepublished normative data from different reference groups. However, we doubt whether a comparison between psychometric tests and electrophysiological tests is justified, because these tests probably assess different components of encephalopathy.[44] If SHE is a preclinical stage of HE, theoretically the diagnostic tests should correlate with the severity of liver disease and the degree (level and/or duration) of exposure to causative factors. In our study, age and severity of liver disease were significantly different in patients with or without abnormal psychometric tests. However, only age appeared to be significant after multivariate analysis. Age, arterial ammonia concentration, Child-Pugh grade, and alcohol as a cause of cirrhosis were significantly different for patients with or without an abnormal spectral EEG. After multivariate analysis only the patients' age and the arterial ammonia concentration were significant. This result, in association with the re-emergence of ammonia as one of the major factors in the pathogenesis of HE,[1] strongly supports the use of spectral EEG in the detection of SHE. In a previous study,[27] we did not find an age effect on the EEG in healthy controls, although common wisdom suggests that aging is associated with slowing of the EEG. Recent studies contradict this opinion and attribute the result of EEG slowing to age-related pathology (e.g., dementia, psychiatric illnesses, and hypertension) rather than to aging itself.[45] Quantified EEG studies in subjects carefully screened for cognitive disturbances fail to show substantial slowing of the EEG with age[46-48]; only marked EEG changes in patients older than 80 years are described.[49] A possible explanation for the higher prevalence of SHE in the older patients could be that the aged brain is more prone to develop HE than the younger. In addition, the older brain may have been exposed for a longer time to the factors causing HE and subsequently have developed more severe cerebral impairment.[10] Our study strengthens this hypothesis as we found a higher prevalence of abnormal EEGs in middle-aged patients compared with younger patients with an equal arterial ammonia concentration (Fig. 2).

Acknowledgment: The authors would like to thank the EEG technicians and Mr. A. Mus of the Department of Clinical Neurophysiology of the University Hospital Dijkzigt, Rotterdam, The Netherlands, for their expert technical assistance.

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