SUBCLINICAL HEPATIC ENCEPHALOPATHY: DIAGNOSIS, CLINICAL IMPLICATIONS, AND INTERVENTION

J.C. QUERO GUILLEN

Cover designed by Rafael Algar Castillo

SUBCLINICAL HEPATIC ENCEPHALOPATHY: DIAGNOSIS, CLINICAL IMPLICATIONS, AND INTERVENTION

SUBKLINISCHE HEPATISCHE ENCEFALOPATHIE: DIAGNOSTIEK, KLINISCHE BETEKENIS EN INTERVENTIE

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de
rector magnificus

Prof. Dr P.W.C Akkermans M.A.

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 7 mei 1997 om 15.45 uur

door

Juan Carlos Quero Guillen
geboren te Melilla

PROMOTIECOMMISSIE

Promotor:	Prof. Dr S.W. Schalm
Overige leden:	Prof. J.H.P. Wilson
	Prof. Dr C.H. Gips
	Prof. Dr J. Passchier

Para mis padres,
Rubichi,
y Rosa Maria

LIST OF ABBREVATIONS

BAC II	Blood Ammonia Checker II
BAEP	brain stem auditory evoked potentials
BCAA	branched-chain amino acids
Bl Des	Block Design Test
CI	confidence interval
CRTS	Choice Reaction Time to Sound
DST	Digit Symbol Test
EEG	electroencephalogram
GABA	gamma amino butyric acid
HE	hepatic encephalopathy
MDF	mean dominant frequency
NCT-A	Number Connection Test part A
NCT-B	Number Connection Test part B
P300	P300 event-related potentials
PBC	primary biliary cirrhosis
PSE-index	portal systemic encephalopathy index
SDT	Symbol Digit Test
SHE	subclinical hepatic encephalopathy
SIP	Sickness Impact Profile
SRTL	Simple Reaction Time to Light
SSEP	somatosensory evoked potentials
SWN	speed of writing numbers test
SWW	speed of writing words test
TMT-A	Trail Making Test part A
TMT-B	Trail Making Test part B
VEP	visual evoked potentials
WAIS	Wechsler Adult Intelligence Scale

CONTENTS

Chapter 1

SUBCLINICAL HEPATIC ENCEPHALOPATHY. AN INTRODUCTION

The contents of this chapter have been published in:
Seminars in Liver Disease (1996, 16: 241-248) under the title Subclinical Hepatic Encephalopathy with the following authors: J.C. Quero and S.W. Schalm.

INTRODUCTION

Hepatic encephalopathy (HE) is traditionally graded into four clinical stages of severity, ranging from lethargy, sleep and memory disturbances (grade 1) to coma (grade 4).[1] In addition to the clinical grading of HE, a subclinical stage has been described. In subclinical hepatic encephalopathy (SHE)* patients with cirrhosis, regardless of its etiology, exhibit various quantifiable neuropsychological defects, but have a normal mental and neurological status on standard clinical examination.[2]

The prevalence of SHE has been reported to vary between 30% to 84% in patients with liver cirrhosis.[3-13] This large variation in prevalence is due to differences in diagnostic methods, patients studied, and definitions of SHE used in the various studies. The diagnosis of SHE may have clinical importance as its presence may have a negative effect on the capacity to perform manual labor,[14] fitness to drive,[15] or quality of life.[16] In view of the reported high prevalence of SHE in patients with cirrhosis and its possible impact on daily life, routine assessment of early stages of HE is recommended,[8] because this syndrome may be reversible with treatment.[4, 17-22]

Because our crude clinical experience, based mainly on outpatient observations, does not confirm the magnitude and severity of SHE as reported in the literature,[2] the aim of this review is to examine critically the clinical significance of this entity, i.e., its prevalence and its impact on the quality of life.

* (other names: subclinical portosystemic encephalopathy (SPSE), latent portosystemic encephalopathy, early hepatic encephalopathy, low-grade portosystemic encephalopathy)

DIAGNOSIS

Up to 64 different diagnostic tests and 8 test batteries for the detection of SHE have been reported in the literature.[23] The diagnostic tests can be roughly divided into two groups: psychometric tests and electrophysiological tests.

Psychometric tests

The hypothesis that mental changes can precede overt neurological symptoms of HE was first proposed by Zeegen et al.[3] They showed that 13 out of 34 patients (38%) without clinical signs of hepatic encephalopathy after portal decompression surgery had an abnormal score in the Reitan trail making tests. Thereafter several psychometric tests have been applied to detect this subclinical stage of HE.[4-13] The number of psychometric tests used in these studies ranged from 1[6] to 24[8] with a mean of 10 tests per study. Tarter et al[16] used a test battery consisting of 26 tests, which took the patient approximately 2.5 hours to complete. To avoid the possible effects of fatigue on the psychometric results, this test battery had to be performed in the course of 2 days.

A common finding of these studies is that psychomotor performance is impaired, while verbal ability is preserved in patients with SHE.[4, 5, 8, 9, 11, 15] The preservation of verbal ability explains the insensitivity of bedside mental status examination in detecting SHE[5]; this finding suggests that white collar workers are less affected by SHE in daily life than blue collar workers,[15] which is in agreement with observations in patients with portal-systemic shunts.[14]

Among the many psychometric tests used for the detection of SHE, four are repeatedly selected because they appear to be of diagnostic value; the Digit

Symbol Test (DST) (Fig. 1), the Block Design Test (Bl Des), the Number Connection Test (NCT), and Reaction Times to Light or Sound (RT).[4, 5, 8, 10-12, 15, 16]

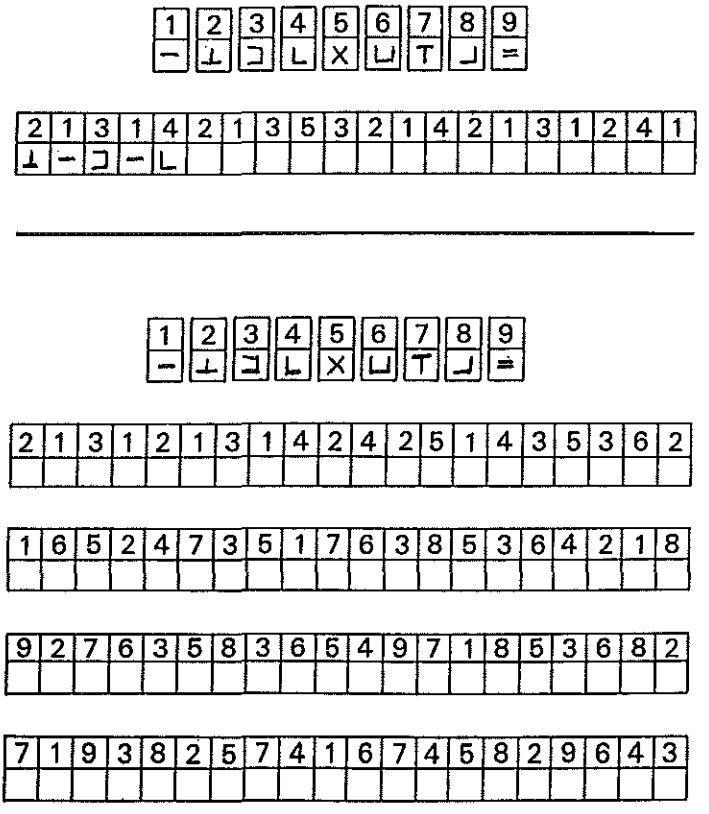

Figure 1: *Digit Symbol Test*: a subtest of the Wechsler Adult Intelligence Scale (WAIS) which measures motor speed and accuracy. The patient is given a list of symbols associated with digits from 1 to 9 and is asked to fill in the blanks with the symbols that correspond to each number. The test score is the total number of correct sequential matchings of digits to symbols in a 90 seconds interval. A high score indicates a good performance.

The NCT-A (Fig. 2) is the most widely used test for the detection of SHE. It is a derivative of the Reitan Trail Test,[24] also known as the Trail

Making Test (TMT). The test is simple to perform, but interpretation of the NCT score is difficult (vide infra).[4-7, 10-12, 25-28] In studies with well defined normal values,[6, 10, 12, 28, 29] abnormal NCT-A scores were observed in 7% to 33% of patients with cirrhosis; abnormal test results were found more frequently in Child-Pugh grade B/C (10%) than in grade A (5%).[29] The results of these studies more closely resemble our clinical impression of a patient population mainly comprised of well-compensated cirrhotics than the very high percentage of abnormal values reported in other studies.

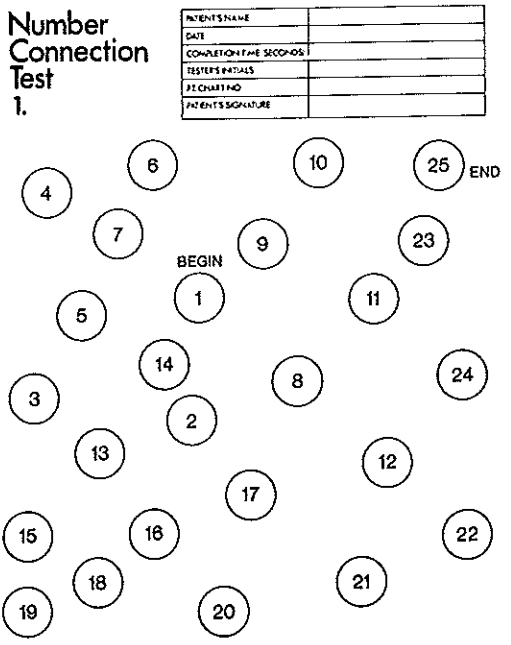

Figure 2: *Number Connection Test part A (NCT-A)*: measures cognitive motor abilities. Subjects have to connect the numbers printed on paper consecutively from 1 to 25, as quickly as possible. Errors are not counted, but patients are instructed to return to the preceding correct number and then carry on. The test score is the time the patient needs to perform the test, including the time needed to correct all errors. A low score represents a good performance.

Pitfalls

It has been demonstrated that psychomotor test scores are influenced by age.[26, 30, 31] Therefore, the use of adequate age normalized values is essential for proper interpretation of psychometric test results (Fig. 3). Most studies do not apply adequate normal values, which could result in a high number of false positives (i.e., patients incorrectly diagnosed as having SHE) in their population. Cut-off criteria, such as that used in the PSE-index[32] which does not take age into account, can give rise to highly misleading results if applied to all age groups.

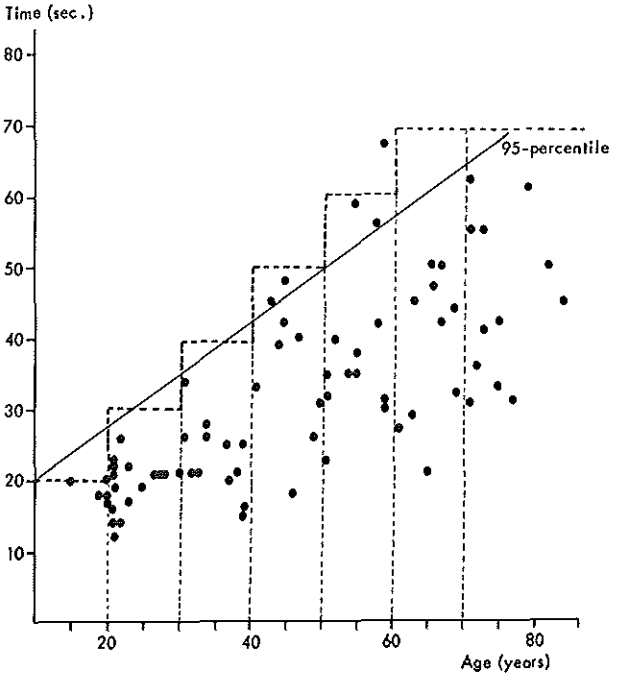

Figure 3: *NCT-A scores for 83 normal invidiuals.* The upper limit of normal is depicted by the solid line (95th percentile; established according to the method of Hogg RV. Estimates of percentile regression lines using salary date. J Amer Statist Assoc 1975; 70: 56-9). The dotted line illustrates the observation that normal values should be less than approximately ten times the subject's age in decades.

Even for studies which take the effect of age into consideration, interpretation of the NCT-A score remains difficult, as published age-corrected normal values vary markedly (Table 1). This can be explained by the difference in normal cut-off points (mean ± 2 SD, 95th percentile), the educational level of the population,[4, 31] and the different versions of the NCT-A used. Although the principle of the NCT-A is always the same (i.e., connecting consecutive numbers from 1 to 25 as quickly as possible), apparently standardized versions of the NCT-A are not equal in difficulty. This was illustrated in 42 consecutive cirrhotic patients without overt HE who performed two different commercially available versions of the NCT (NCT-A supplied by Duphar Laboratories Limited [Southampton, United Kingdom] and NCT-A supplied by Duphar Pharma GmbH & Co [Hannover, Germany[32]]). The mean difference between these tests was 9 seconds (Table 2).

The NCT-B test, in which patients have to connect numbers and letters in consecutive order, has been reported to be one of the most sensitive tests for the detection of SHE.[4, 28] Nevertheless, the specificity of the NCT-B is low, because a considerable proportion of the normal 'heterogeneous' population scores abnormal in this test. Furthermore, the need for normal values corrected for educational status[30] appears even greater for the NCT-B than for the NCT-A. To illustrate this, we asked 83 outpatients with cirrhosis to perform the NCT-B. Seven out of 19 foreign patients were not able to complete the test because of insufficient knowledge of the Roman alphabet. Of the remaining 76 patients 18% scored abnormal in the NCT-B; Dutch speaking foreigners had a test score three times (33%) worse than native Dutch patients (11%) (unpublished data).

Table 1 Normal values (seconds) for various age groups and/or educational levels determined for several versions of the NCT-A.

Trail Making Test						
Age groups (years)		**20 - 39**	**40 - 49**	**50 - 59**	**60 - 69**	**70 - 79 years**
Davies[30] (values expressed as 10th to 90th percentile)		21 -50	22 - 59	25 -67	29 - 104	38 - 168
Age groups (years)			**35 - 50**	**51 - 60**	**61 - 70**	**≥ 71 years**
Marchesini[6] (values expressed as mean ± standard error)	*high education*		28 ± 3	32 ± 3	34 ± 2	
	low education		40 ± 6	46 ± 6	71 ± 9	86 ± 9
Number Connection Test						
Age groups (years)		**< 35**	**35 - 50**	**51 - 60**	**61 - 70**	**≥ 71 years**
Zeneroli[30] (values expressed as mean ± standard deviation)	*high education*	45.3 ± 13.3	56.2 ± 18.3	67.8 ± 19.5		
	low education	51.5 ± 18.3	70.5 ± 28.2	85.9 ± 26.5	143.7 ± 67.2	265.2 ± 58.6
Age groups (years) (values expressed as mean ± standard deviation)		**20 - 39**	**40 - 49**	**50 - 59**	**60 - 69 years**	
Yen[27]		28.3 ± 14.6	32.4 ± 16.1	37.7 ± 15.7	42.1 ± 17.4	

Table 2: Results (in seconds) of two different versions of the NCT-A performed simultaneously by 42 patients with liver cirrhosis without hepatic encephalopathy.

	mean ± SD	*range*	*p value*
NCT-A (Duphar United Kingdom)	42.0 ± 15	20 - 81	< .00001
NCT-A (Duphar Germany)	33.3 ± 13	15 - 66	

Recently, the Figure Connection Test parts A and B (FCT), which can be used to test illiterate individuals, was developed.[34] Results of the FCT were similar to those of the NCT; however, an effect of education could still be demonstrated.

Repetitive testing has also been shown to have an effect on psychometric test scores.[20, 21, 35] To abolish this learning effect during the follow-up of patients with cirrhosis, the use of different test variants of equal difficulty has been suggested.[31]

We conclude, therefore, that psychometric tests are not as simple and easy to interpret as has been suggested. Age, education, and a learning effect must be taken into account when interpreting the results. Furthermore, the term "bedside" tests is misleading because these tests should be performed in a sitting position in a quiet room with sufficient light.

Electrophysiological tests

Due to the above mentioned disadvantages of psychometric tests, several authors have proposed the use of electrophysiological methods as more objective tools for the detection of SHE.[26, 28, 36, 37] Studies have been performed with visual-evoked potentials (VEP),[12, 26, 28, 36-40] brain stem auditory-evoked potentials (BAEP),[37, 38] somatosensory-evoked potentials (SSEP),[27, 37, 38] and P300 event-related potentials (P300) (Fig. 4).[28, 41, 42]

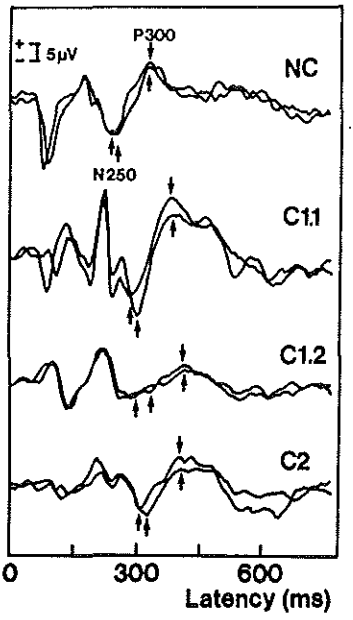

Figure 4: *PFP300 potentials of the B stimuli for one person from each of the study groups.* The N250 and PFP300 latencies are markedly prolonged in the patients with compensated liver cirrhosis (C1.1), decompensated liver cirrhosis (C1.2), and hepatic encephalopathy (C2) compared with the potentials of a patient from the control group (NC); the amplitudes do not change significantly. (Kugler CF, Lotterer E, Petter J, Wensing G, Taghavy A, Hahn EG, Fleig EW. Visual event-related P300 potentials in early portosystemic encephalopathy. Gastroenterology 1992; 103: 302-10). P300 is defined as the first positive going peak after the N1-P2-N2 complex between 250 and 500 msec after presentation of the stimulus.

The percentage abnormal results among cirrhotics without overt hepatic encephalopathy found in the various studies ranged from 0% to 63% for VEP, 0% to 41% for BAEP, 5% to 34 % for SSEP, and 14% to 78% for P300. Although evoked potentials seem less sensitive than psychometric tests, a higher specificity and positive predictive value has been suggested by Yen et al,[27] who found that a larger percentage of patients with abnormal SSEP developed clinical overt HE compared with patients with an abnormal NCT-A. The results of these studies are apparently influenced by the different methodologies and patient populations studied. A detailed review of these evoked potentials studies has been published recently.[43] In the last few years, the diagnostic value of the P300 latency has emerged, whereas confirmation of the diagnostic value of other types of evoked potentials has been very limited. The broad overlap of the evoked potentials results found in cirrhotic patients and healthy controls makes interpretation particularly difficult.[39] In contrast to the conventional evoked potentials, the response on event-related endogeneous evoked potentials, such as the P300, does not depend on the physical properties of the stimulus, but rather on the meaning of the stimulus to the patient. In P300 potentials, for example, the patients response to two different stimuli is measured. P300 potentials are therefore considered sensitive in reflecting subtle cognitive dysfunction because they are electrophysiological markers of cognitive processes such as stimulus discrimination and evaluation.

The electroencephalograph (EEG) has not played a major role in the diagnosis of SHE. However, the percentage abnormal EEGs among cirrhotics without HE varies from 8% to 35%,[4, 8, 14, 26, 28, 39, 44] which is still a considerable proportion of the cirrhotic population. Furthermore, when adequate age-

corrected normal values are used for psychometric tests, the EEG yields two to three times more abnormal results than the NCT-A![28, 29] We prefer spectral analysis of the EEG (Fig. 5) above conventional EEG, because the former is less susceptible to interobserver or intraobserver variability and provides easily interpretable quantitative data. For the diagnosis of SHE, an elevated percentage theta activity is used.[44]

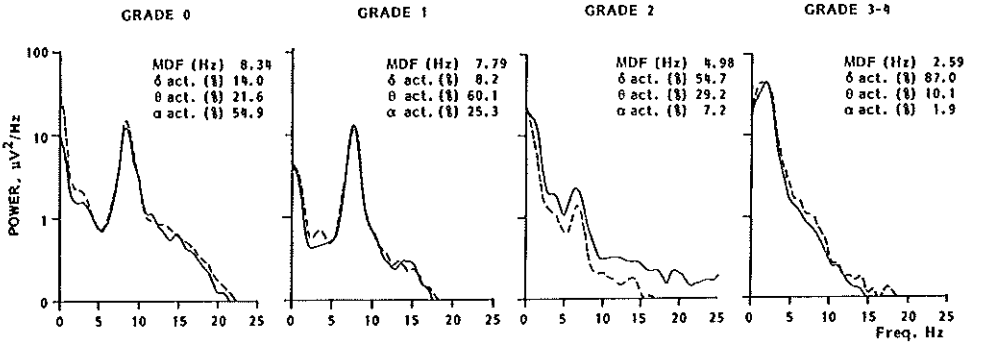

Figure 5: *Examples of EEG power spectra for different grades of hepatic encephalopathy.* Power spectra of cirrhotic patients without encephalopathy resemble those of healthy controls. The mean dominant frequency (MDF) decreases with increasing clinical grade of encephalopathy (peak frequency shifts to the left); MDF alone, however, cannot be used as a single parameter to grade hepatic encephalopathy. Grade 0 and grade 1 (both MDF $\geq$ 6.4 c/sec) can be differentiated by means of the increased percentage of theta activity ($\geq$ 35%) in grade 1. Patients with grade 1 and some with grade 2 abnormalities may lack clinical signs of hepatic encephalopathy, and are diagnosed as having subclinical hepatic encephalopathy (35% in this study). Patients with grade 3 to 4 can be differentiated from grade 2 by means of the increased percentage of delta activity ($\geq$ 70%). (Van der Rijt CCD, Schalm SW, de Groot GH, de Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph Clin Neurophysiol 1984; 57: 423-6)

Pitfalls

An obvious disadvantage of electrophysiological tests compared with psychometric tests is the need for expensive, sophisticated equipment and well-trained personnel. Furthermore, the results should be interpreted by experienced neurophysiologists. Although spectral analysis of the EEG, according to Van der Rijt et al,[44] can be interpreted by a non-neurologist, quality control by neurophysiologists is still needed. In addition, the results of spectral EEG analysis reported in the literature cannot be compared because of differences in methodology, such as bandwidth and filters.[20, 28, 44] Methodological variations are even larger for evoked potentials.

Several investigators have used a combination of psychometric and electrophysiological tests for the diagnosis of SHE.[4, 14, 27, 28, 39, 44] Their results show that there is not a complete overlap of abnormal psychometric and electrophysiological test results. Therefore, a combination of psychometric and electrophysiological tests should be used for the detection of SHE because each method probably assesses a different brain function.

CLINICAL SIGNIFICANCE

Implications for daily life

Since consciousness is not disturbed, the clinical significance of SHE is less obvious than that of overt HE. The characteristics of SHE are impaired psychomotor performance with preserved verbal ability. Kardel et al[14] have shown that impaired psychomotor performance has more implications for

patients performing manual work than those involved in intellectually demanding work. In addition, Schomerus et al[15] postulated that the psychomotor defects found in patients with SHE could have a negative effect on fitness to drive. They performed a study in which 40 patients with cirrhosis, divided into three groups (alcoholic cirrhosis, nonalcoholic cirrhosis, cirrhotics with minor EEG changes), and a control group of patients with alcoholic pancreatitis underwent an extensive neuropsychological test battery (24 tests, 102 variables studied!). On the basis of the results of this neuropsychological examination, the investigators concluded that 60% of the cirrhotics were unfit to drive a car and that the driving capacity of 25% was questionable. Of the cirrhotic patients with minor EEG changes, 90% were considered unfit to drive. Unfortunately, the authors do not describe the method used to assess driving fitness in their article, which makes their conclusions less convincing.

Doubts about whether an impaired fitness to drive exists in SHE has been markedly boosted by two recent publications.[45, 46] O'Neill[45] reported little correlation between psychometric tests and driving ability, and suggested using 'activity of daily living scales' for this purpose. Srivastava et al[46] performed a study in which the driving fitness of 15 patients with liver cirrhosis was assessed "on the road". The investigators used the five tests most highly recommended in the literature (Bl Des, DST, NCT-A, NCT-B, Visual Reaction Time) to diagnose SHE. Driving fitness was assessed not only by a simulator, but also by a real driver's examination in an automobile. Patients with liver cirrhosis and SHE (n=9) did not drive less well when compared with 15 healthy controls. A remarkable finding of this study was one patient (a taxi driver!) who had extremely bad psychometric test results but gave a good driving performance.

Another way of evaluating the clinical implications of SHE is questionnaires that measure the effect of illness on daily life.[16, 17] Tarter et al[16] measured quality of life among 30 patients with liver cirrhosis using the Sickness Impact Profile (SIP) questionnaire. Cirrhotic patients reported more impairment in several SIP categories (sleep and rest, recreation and pastimes, body care and movement) compared with 10 patients with Crohn's disease. Recently, we have confirmed their findings, comparing 26 cirrhotic patients with SHE with 57 cirrhotic patients without SHE.[47] A study is in progress to determine whether the diminished quality of life is due to SHE or to the diminished liver function in these patients.

Natural History

Although it is theoretically assumed that SHE will develop into clinically overt HE, few long-term follow-up studies have been performed to document this sequence.

In a noncontrolled study, three out of nine cirrhotic patients with SHE developed HE during a one-year follow-up period.[4] All patients had a surgical portal-systemic shunt, which is in itself a major risk factor for HE. Yen et al[27] performed a 6-month follow-up study of 44 patients with decompensated liver cirrhosis. Fifty percent of these patients developed HE within 6 months, illustrating the severity of the liver disease. Significantly, more patients with abnormal NCT-A or SSEP on initial examination developed overt HE (72%) than patients without abnormalities (21%). The specificity of the SSEP was considered higher than that of the NCT-A, as only 5% of the patients without HE had an abnormal SSEP, whereas 32% had an abnormal NCT-A.

TREATMENT

Several intervention studies using nonabsorbable saccharides,[17-19] dietary manipulation,[4, 20] and branched-chain amino acids (BCAA)[21, 22] have been reported, all of which document some improvement in SHE after treatment.

Nonabsorbable saccharides

For the treatment of SHE, McClain et al[17] compared lactulose with a placebo in 32 patients with liver cirrhosis. Patients were treated for 3 months. In both treatment groups the medication dose was titrated to achieve three soft stools daily. Efficacy of treatment was assessed with five psychometric tests (Trailmaking Tests A and B [TMT-A, TMT-B], Speed of Writing Words and Numbers [SWW, SWN], and the Digit Symbol Test [DST]). Patients were not preselected on the basis of abnormal psychometric tests. In addition, the Katz Social Inventory was used to assess how these patients functioned within their environment. Ten patients dropped out of the study, leaving a total of 10 evaluable patients in the lactulose group and 12 patients in the placebo group. There was a significant 11% to 20% improvement in three out of five psychometric tests (TMT-A, SWW, DST) in the treatment group compared with baseline values. No improvement in psychometric tests was seen in the placebo group. In addition, neither the lactulose nor the placebo group showed an improvement in daily functioning as measured by the Katz Social Inventory score.

Morgan et al[18] performed a randomized cross-over study with lactulose and lactitol in 20 stable patients with liver cirrhosis. Patients were randomized to receive either lactulose or lactitol for 2 months; after a wash-out period of

4 weeks they crossed over to the other saccharide and were treated for an additional 2 months. The medication dose was adjusted to produce two semi-soft stools daily. Efficacy of treatment was assessed using conventional EEG and five psychometric tests (NCT, DST, Digit Copying [DC], two-choice visual reaction time test, perceptual maze test). All patients had abnormal scores for at least two psychometric tests at baseline evaluation. Six patients dropped out of the study, leaving a total of 14 evaluable patients. Both lactulose and lactitol showed only significant improvement in the Digit Symbol test.

Salerno et al[19] studied the long-term efficacy of two dosage schedules of lactitol in SHE. Twenty-eight patients were randomized to receive either 0.3 g/kg or 0.5 g/kg bodyweight lactitol daily for 5 months. Treatment efficacy was assessed by venous ammonia levels, EEG, psychometric tests (NCT, DST, cancelling As), and the PSE-index. All patients had SHE, defined as at least two abnormal psychometric tests. Six patients dropped out of the study, leaving 11 evaluable patients in each treatment group. Both the low-dose and high-dose lactitol groups showed significant improvement in the venous ammonia levels and cancelling As test. Improvement in the NCT and DST was found only for patients on high-dose lactitol. All efficacy parameters returned to baseline values 1 month after treatment. Subjective improvement in concentration was reported by only 2 out of 11 patients on high-dose lactitol.

Dietary manipulation

Rikkers et al[4] were the first to document reversibility of neuropsychological abnormalities after treatment. In this open study, five postshunt cirrhotic patients were put on an isocaloric zero protein diet for 7 days after a 2-week baseline period on a 40 g/day protein diet. Efficacy

parameters were four psychometric tests (TMT-A and B, Simple Reaction Time to Light [SRTL], Choice Reaction Time to Sound [CRTS]) and fasting plasma ammonia. A significant improvement after treatment was found for three psychometric tests (TMT-A and B, CRTS) and the ammonia concentration.

De Bruijn et al[20] performed a cross-over study with eight patients with a surgical portal-systemic shunt, who received an animal, vegetable, or mixed protein diet for 1 week. Treatment efficacy was assessed with EEG (conventional and computerized) and the Trailmaking Tests A and B. Compared with the animal protein diet, the vegetable protein diet gave an improvement in the peak frequency of the computerized EEG. There was not a significant difference in either the TMT-A and B or the conventional EEG between the various diet groups.

Branched-chain amino acids

Egberts et al[21] performed a cross-over study with oral BCAA using 22 patients with liver cirrhosis without clinical signs of HE. In all cases, impaired driving capacity was suspected. Patients received either BCAA or placebo for 1 week and then crossed over to the other treatment group. Laboratory and clinical examinations were performed on the first and last days of each treatment period and 4 weeks after the last treatment day. Efficacy of treatment was assessed by venous ammonia levels, EEG, and a neuropsychological test battery consisting of 15 tests. In addition, driving capacity was assessed on the basis of the psychometric test results. No significant decrease in the ammonia level or improvement in the EEG was seen after treatment with BCAA. Seven out of 15 psychometric tests improved during BCAA treatment; 5 out of 15 tests deteriorated 4 weeks after the BCAA treatment period. A remarkable

finding of this study was the fact that three psychometric tests (NCT, Number Revision Test, d2 test) showed statistically significant improvement due to a learning effect. Driving capacity did not change significantly with BCAA.

The long-term effects of BCAA in SHE were studied by Plauth et al.[22] Twenty-three patients with liver cirrhosis and suspected impaired driving capacity were treated for 8 weeks in a placebo-controlled cross-over study. Efficacy parameters were venous ammonia levels, a neuropsychological test battery, and assessment of driving capacity. Due to 6 dropouts, 17 patients were evaluable. Compared to the placebo, BCAA treatment resulted in a significant improvement in 3 (DST, Digit Table, long pins) out of 12 psychometric tests. The NCT was susceptible to a significant learning effect in both groups; however, there was no difference in improvement between BCAA and placebo. Long-term BCAA treatment did result in a significant improvement in driving capacity.

Does treatment of SHE improve daily functioning and does it prevent the development of clinically overt HE? The abovementioned studies[4, 17-21] demonstrated moderate improvement in fewer than half of the psychometric tests performed. In addition, only three studies[17, 20, 21] assessed whether treatment was effective against the assumed social and clinical complications of SHE. One of these studies concluded that long-term treatment of SHE improves driving capacity[22]; however, the methodology of assessing driving capacity is not described and, therefore, immediate acceptance of such a conclusion is not justified.

DISCUSSION

Subclinical hepatic encephalopathy is an entity which was first described in the early 1970s in patients with a portal-systemic shunt.[3, 4, 14] Evidence shows that psychomotor performance is disturbed in patients with SHE and that cognitive[15] or subcortical[48] impairment is responsible. However, the application of various diagnostic methods has caused confusion regarding the incidence and significance of SHE.

The reported prevalence of SHE depends on the kind and number of diagnostic tests, the population tested, and the definition of SHE used. The prevalence of abnormal psychometric tests is much lower when adequate age-related percentile scores are used. If adequate normal values are used, then less than 10% of the patients will usually have an abnormal score for the NCT-A.[12, 28, 29] A combination of various tests as a diagnostic screen for SHE has been suggested by several authors.[2, 12, 28] Among the proposed psychometric tests are the NCT-A, NCT-B, Digit Symbol Test, Block Design Test, and Reaction Times to Light or Sound. The first three tests are easily administered "pencil and paper" tests, which can be performed during an outpatient control visit. The problem with these tests lies in the interpretation of the test score; age-adjusted normal values for the test are a minimum requirement. Even then, the NCT-B is not generally applicable to the entire population because of its strong educational and cultural bias.

Should we use psychometric tests, electrophysiological tests, or a combination of both to detect SHE? Psychometric tests seem more sensitive than electrophysiological tests, but their specificity is probably lower.[15, 27] In addition, complete overlap between abnormal psychometric test results and

abnormal electrophysiological tests does not exist. This suggests that a combination of these two methods should be used for the detection of SHE.

The psychometric and electrophysiological diagnostic tests which should be used depends on local circumstances and experience. Weissenborn et al[28] suggest the NCT-B and P300 evoked potentials for detecting SHE. We have chosen to use the NCT-A, SDT, and spectral-EEG as diagnostic tools.

We define SHE as an abnormal electrophysiological test and/or psychometric test. This is an arbitrary definition, since there is no 'gold standard' for diagnosis. A good diagnostic test should tell us something about the severity of the disease, the subsequent clinical course or prognosis of the disease, and the response to therapy.[49] How do these criteria apply to the diagnostic tests used for the detection of SHE?

SHE does seem to correlate with liver function[4, 5, 12, 15, 50, 51] and is found more often among patients with more severe liver disease.[12, 29] Therefore, development of SHE into clinically overt HE is likely. However, it must yet be determined whether SHE offers additional information on the clinical course and prognosis of the disease compared with the simple and fully investigated Child-Pugh classification.

Should we diagnose and treat SHE because the impaired performance skills could be dangerous for the patient and society? Treatment of SHE may be beneficial for cirrhotic patients with stable liver disease and impaired performance at work or in daily life. However, only a minority of these patients have SHE, and not all of them will experience an impaired quality of life. In patients with SHE and progressive liver disease, treatment should be directed towards improvement of liver function (e.g. antiviral therapy, transplantation), as this appears to determine the quality of life and prognosis rather than SHE

itself.

Further studies, in which the clinical relevance of this subclinical entity is evaluated, are needed before more widespread treatment of SHE can be recommended.

REFERENCES

1. Parsons-Smith BG, Summerskill WHJ, Dawson AM, Sherlock S. The electroencephalopgraph in liver disease. Lancet 1957; 2: 867-871.
2. Gitlin N. Subclinical portal-systemic encephalopathy. Am J Gastroenterol 1988; 82:8-11.
3. Zeegen R, Drinkwater JE, Dawson AM. Method for measuring cerebral dysfunction in patients with liver disease. Br Med J 1970; 2: 633-636.
4. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 1978; 75: 462-469.
5. Gilberstadt SJ, Gilberstadt H, Zieve L, Buegel B, Collier RO, McClain CJ. Psychomotor performance defects in cirrhotic patients without overt encephalopathy. Arch Intern Med 1980; 140: 519-521.
6. Marchesini G, Zoli M, Dondi C, Cecchini L, Angiolini A, Bianchi FB, Pisi E. Prevalence of subclinical hepatic encephalopathy in cirrhotics and relationship to plasma amino acid balance. Dig Dis Sci 1980; 25: 763-768.
7. Loguercio C, Del Vechio-Blanco C, Coltorti M. Psychometric tests and latent portal-systemic encephalopathy. Br J Clin Pract 1984; 38: 407-411.
8. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, non-shunted patients with cirrhosis. J Hepatol 1986; 3: 75-82.
9. Joelsson B, Aslund U, Hultberg B, Alwmark A, Gullstrand P, Bengmark S. Portal-systemic encephalopathy. Influence of shunt surgery and relations to serum amino acids. Scand J Gastroenterol 1986; 21: 900-906.
10. Moore JW, Dunk AA, Crawford JR, Deans H, Besson JAO, De Lacey G, Sinclair TS, Mowat NAG, Brunt PW. Neuropsychological deficits and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis. J Hepatol 1989; 9: 319-325.
11. Sood GK, Sarin SK, Mahaptra J, Broor SL. Comparative efficacy of psychometric tests in detection of subclinical hepatic encephalopathy in nonalcoholic cirrhotics: search for a rational approach. Am J Gastroenterol 1989; 2: 156-159.
12. Koch H, Schauder P, Schäfer G, Dahme B, Ebel W, Vahldiek B, König F, Henning H, Untersuchungen zur diagnose und prävalenz der latenten hepatischen encephalopathie. Z Gastroenterol 1990; 28: 610-615.

13. Schomerus H, Schreiegg J. Prevalence of latent portasystemic encephalopathy in an unselected population of patients with liver cirrhosis in general practice. Z Gastroenterol 1993; 31: 231-234.
14. Kardel T, Lund Y, Zander Olsen P, Möllgaard V, Gammeltoft A. Encephalopathy and portocaval anastomosis. Scand J Gastroenterol 1970; 5: 681-685.
15. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Döll W. Latent portasystemic encepalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981; 26: 622-630.
16. Tarter RE, Hegedus AM, van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. Gastroenterology 1984; 86: 1421-1427.
17. McClain CJ, Potter TJ, Kromhout JP, Zieve L. The effect of lactulose on psychomotor performance tests in alcoholic cirrhotics without overt hepatic encephalopathy. J Clin Gastroenterol 1984; 6: 325-329.
18. Morgan MY, Alonso M, Stanger LC. Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. J Hepatol 1989; 8: 208-217.
19. Salerno F, Moser P, Maggi A, Vitaliani G, Benetti G. Effects of long-term administration of low-dose lactitol in patients with cirrhosis but without overt encephalopathy. J Hepatol 1994; 21:1092-1096.
20. De Bruijn KM Blendis LM, Zilm DH Carlen PL, Anderson GH. Effect of dietary protein manipulations in subclinical portal-systemic encephalopathy. Gut 1983; 24: 53-60.
21. Egberts EH, Schomerus H, Hamster W, Jürgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. Gastroenterology 1985; 88: 887-895.
22. Plauth M, Egberts EH, Hamster W, Török M, Müller PH, Brand O, Fürst P, Dölle W. Long-term treatment of latent portosystemic encephalopathy with branched-chain amino acids. A double-blind placebo-controlled crossover study. J Hepatol 1993; 17: 308-314.
23. Conn HO. Subclinical hepatic encephalopathy. In: Hepatic encephalopathy: Syndromes and Therapies. Conn HO, Bircher J eds. Bloomington, Illinois: Medi-Ed Press, 1994: 27-39.
24. Reitan RM. Validity of the trail making test as an indication of organic brain damage. Percept Mot Skills 1958; 8: 271-276.
25. Sarin SK, Nundy S. Subclinical encephalopathy after portosystemic shunts in patients with non-cirrhotic portal fibrosis. Liver 1985; 5: 142-146.

26. Levy LJ, Bolton RP, Losowsky MS. The use of the visual evoked potential (VEP) in delineating a state of subclinical hepatic encephalopathy. A comparison with the number connection test. J Hepatol 1987; 5: 211-217.
27. Yen CL, Liaw YF. Somatosensory evoked potentials and number connection test in the detection of subclinical hepatic encephalopathy. Hepatogastroenterol 1990; 37: 332-334.
28. Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Künkel H. Neurophysiological assessment of early hepatic encephalopathy. Electroenceph Clin Neurophysiol 1990; 75: 289-295.
29. Hartmann IJC, Quero JC, Schalm SW. Diagnosis of subclinical hepatic encephalopathy: spectral-EEG versus standard psychometric tests. Gastroenterology 1995; 108: A1080
30. Davies ADM. The influence of age on Trail Making Test performance. J Clin Psychology 1968; 24: 96-98.
31. Zeneroli ML, Cioni G, Ventura P, Russo AM, Venturini I, Casalgrandi G, Ventura E. Interindividual variability of the number connection test. J Hepatol 1992; 15: 263-264.
32. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. Gastroenterology 1977; 72: 573-583.
33. Hamster W, Kluck M, Schomerus H. PSE-Syndrom-Test. Kurzform. Beltz Test Gesellschaft, Weinheim. 1985
34. Dhiman RK, Saraswat VA, Verma M, Naik SR. Figure connection test: a universal test for assessment of mental state. J Gastroenterol Hepatol 1995; 10: 14-23.
35. Conn HO. Trailmaking and number-connection tests in the assessment of mental state in portal systemic encephalopathy. Am J Dig Dis 1977; 22: 541-550.
36. Zeneroli ML, Pinelli G, Gollini G, Penne A, Messori E, Zani G, Ventura E. Visual evoked potential: a diagnostic tool for the assessment of hepatic encephalopathy. Gut 1984; 25: 291-299.
37. Mehndirrata MM, Sood GK, Sarin SK, Gupta M. Comparative evaluation of visual, somatosensory, and auditory evoked potentials in the detection of subclinical hepatic encephalopathy in patients with nonalcoholic cirrhosis. Am J Gastroenterol 1990; 85: 799-803.
38. Sandford SL, Tarter RE, Sclabassi R, Van Thiel DH. Sensory information processing in patients with nonalcoholic cirrhosis. Short-latency visual, auditory, and somatosensory event-related potentials. J Neurol Sci 1987; 80: 269-276.

39. Johansson U, Andersson T, Persson A, Eriksson LS. Visual evoked potential - a tool in the diagnosis of hepatic encephalopathy? J Hepatol 1989; 9: 227-233.
40. Davies MG, Rowan MJ, Feely J. Flash visual evoked responses in the early encephalopathy of chronic liver disease. Scand J Gastroenterol 1990; 25: 1205-1214.
41. Davies MG, Rowan MJ, MacMathuna P, Keeling PWN, Weir DG, Feely J. The auditory P300 event-related potential: an objective marker of the encephalopathy of chronic liver disease. Hepatology 1990; 12: 688-694.
42. Kugler CF, Lotterer E, Petter J, Wensing G, Taghavy A, Hahn EG, Fleig EW. Visual event-related P300 potentials in early portosystemic encephalopathy. Gastroenterology 1992; 103: 302-310.
43. Kullman F, Hollerbach S, Holstege A, Scholmerich J. Subclinical hepatic encephalopathy: the diagnostic value of evoked potentials. J Hepatol 1995; 22: 101-110.
44. Van der Rijt CCD, Schalm SW, de Groot GH, de Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph Clin Neurophysiol 1984; 57: 423-426.
45. O' Neill D. Physicians, elderly drivers and dementia. Lancet 1992; 41-43.
46. Srivastava A, Mehta R, Rothke SP, Rademaker AW, Blei AT. Fitness to drive in patients with cirrhosis and portal-systemic shunting: a pilot study evaluating driving performance. J Hepatol 1994; 21: 1023-1028.
47. Quero JC, De Bruijn I, Hartmann IJC, Schalm SW. Does subclinical hepatic encephalopathy affect quality of life? Gastroenterology 1995; 108: A1151.
48. Kono I, Ueda Y, Nakajima K, Araki K, Kagawa K, Kashima K. Subcortical impairment in subclinical hepatic encephalopathy. J Neurol Sci 1994; 126: 162-167.
49. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. The selection of diagnostic tests. In: Clinical epidemiology, a basic science for clinical medicine. Little, Brown and Company. USA 1991.
50. Tarter RE, Sandford SL, Hays AL, Carra JP. Hepatic injury correlates with neuropsychologic impairment. Intern J Neurosci 1989; 44: 75-82.
51. Pérez-Cuadrado Martínez E, Silva González C, Robles Reyes A. Variabilidad y alargamiento del tiempo de reacción en el diagnóstico precoz de la encefalopatía hepática subclínica. Rev Esp Enf Digest 1990; 77: 29-32.

Chapter 2

DETERMINATION OF AMMONIA IN CAPILLARY AND ARTERIAL BLOOD SIMULTANEOUSLY USING THE BLOOD AMMONIA CHECKER II

The contents of this chapter have been published in:
Advances in hepatic encephalopathy and metabolic nitrogen exchange, Capocaccia L, Merli M, Riggio O (Eds.), CRC Press, Boca Raton, USA (1995; 414-420) under the same title with the following authors: J.C. Quero, J.R. Huizenga, R.A.F.M. Chamuleau, B.G. Blijenberg, C.H. Gips, S.W. Schalm.

INTRODUCTION

The ammonia determination in arterial blood correlates best with the severity of hepatic encephalopathy.[1] Arterial punctures for investigational purposes, however, can cause medical ethical problems in some european countries.

Recently, the Blood Ammonia Checker (BAC) II has been introduced, which determines blood ammonia quantitatively in 20 μl of blood.[2-4] Because of the small amount of blood needed, this apparatus is suitable for measuring the ammonia content in capillary blood. However, it needs to be investigated whether capillary blood ammonia levels correspond closely to arterial ammonia levels and if they are reliable in monitoring patients with liver disease.

We present the results of a pilot study comparing capillary with arterial ammonia levels in patients with liver disease and controls using the BAC II system.

MATERIALS AND METHODS

Microdiffusion method

The Blood Ammonia Checker (BAC) II system (Kyoto Daiichi Co., Ltd., Kyoto, Japan) consists of a reflectance meter and special reagent strips for blood ammonia determinations. The method is based on alkaline liberation of gaseous ammonia, passage of gaseous ammonia through the pores of a so-called spacer and finally bromocresol colouring and colorimetry.

The method uses 20 μl of whole blood and after exactly 200 seconds the

result can be read. This BAC II can be used as a bedside procedure.
The arterial blood ammonia reference values using this method amounted to 7 - 28, median 21 μmol/l.[2, 3]

Reference methods

For reference two enzymatic methods based on the same enzymatic conversion of NADPH to $NADP^+$ have been used, viz. the Du Pont aca method and the Boehringer Mannheim procedure.[5] Reference values for the arterial ammonia concentration using these methods are 10 - 30 μmol/l and 9 - 37 μmol/l, respectively. In contrast to the BAC II method, both enzymatic methods measure ammonia in plasma.

Subjects

The comparison of the ammonia content in capillary and arterial blood was performed in 12 controls without liver disease (6 healthy volunteers and 6 lung patients in which arterial puncture was done for routine blood gas analyses) and 16 patients with liver disease, portosystemic shunting and elevated NH_3 or with acute liver failure.

Serial measurements of ammonia in capillary blood for 3 days was performed in 14 fasting healthy controls.

Procedure for drawing capillary blood

The fingertip was cleansed thoroughly because sweat has been reported to have a high ammonia content of about 3 mmol/l, which is 100-200 times higher than normally found in blood.[6] After thoroughly washing the hands with water (in a few patients also with soap), the finger was cleaned with

chlorhexidin in 70 % alcohol and dried using a dry tissue (Medipress, Van Heek Medical, Losser, Holland). The fingertip was pricked with an automatic lancing device (Ames Autolet, Owen Mumford Ltd., Woodstock, England) and cleaned after the first drop of blood using a dry tissue. Twenty μl of the second drop of blood was taken with an Eppendorf pipette with Eppendorf disposable tips for the NH_3 determination with the BAC II.

Procedure for drawing arterial blood

Arterial puncture was performed in the radial artery in the hyperextended wrist using a 2.0 ml syringe with a 0.6 mm x 16 mm needle (both Monoject, Sherwood Medical, Ballymoney, Northern Ireland). Prior to the puncture the syringe was flushed with 1 drop sodium-heparin (Thromboliquine, Organon Teknika, Oss, The Netherlands). After drawing blood the syringe was gently rotated and immediately placed on crushed ice. Approximately 0.1 ml blood was transferred from the syringe to a 1.5 ml Eppendorf micro test tube. Twenty μl blood was taken with an Eppendorf pipette from this tube and used for the bedside NH_3 determination with the BAC II. The remaining blood in the syringe was used for the lab based NH_3 determination with the 'Du Pont Automatic Clinical Analyzer (aca)' procedure (only in Rotterdam). In 6 controls from the University Hospital Groningen the arterial NH_3 was measured with the 'Boehringer Mannheim' procedure.

Capillary and arterial blood was drawn in the morning in the fasting patient within a 10 - minute period. Bedside and lab based measurements were done within 15 minutes.

RESULTS

Table 1 shows the results of the ammonia measurement in capillary and arterial blood. The mean difference between capillary and arterial ammonia measured with the BAC II was 33 μmol/l (SD 23.5, range 2 - 71 μmol/l) in controls and 23 μmol/l (SD 26.2, range -27 - 68 μmol/l) in patients with liver disease. The mean difference between arterial ammonia measured with the BAC II and the enzymatic procedures in the control and patient group was 6 μmol/l (SD 11.0, range -8 - 33 μmol/l) and 10 μmol/l (SD 21.1, range -27 - 45 μmol/l) respectively.

Table 1: Capillary versus arterial ammonia (μmol/l) measured with the BAC II and enzymatic methods ('aca' or 'Boehringer-Mannheim' procedure) in 12 controls and 12 patients with cirrhosis of the liver and portosystemic shunting.

	mean	range	SD	mean	range	SD
	Controls			*Patients*		
Capillary NH_3 (BAC II)	64	24-102	25.1	161	88-286*	69.0
Arterial NH_3 (BAC II)	31	15-57	10.5	141	3-286*	73.1
Arterial NH_3 (enzymatic)	26	12-43	7.7	131	62-302	69.7

* Upper detection limit of the BAC II apparatus.

Figure 1 illustrates the relation between capillary and arterial ammonia levels in both groups. Capillary and arterial ammonia BAC values of both groups are plotted in Figure 2. Although we found a reasonable correlation (r = 0.92) between capillary and arterial ammonia levels measured with the BAC II, the difference in the mean concentration in capillary and arterial blood was statistically significant (p = 0.0005 in the controls, p = 0.004 in the patients, paired t-test). The differences between the arterial ammonia levels measured with the BAC II and the enzymatic procedures were not statistically significant (p = 0.11 in the controls, p = 0.13 in the patients, paired t-test).

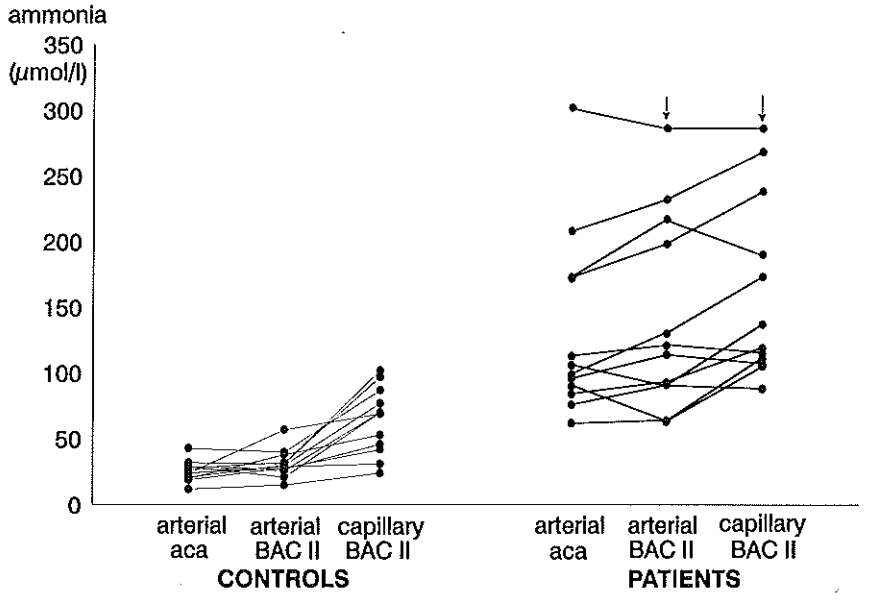

Figure 1: Values for arterial (determined with the BAC II and enzymatically) and capillary ammonia levels (only determined with the BAC II) in 12 controls and 12 patients (arrows indicate the upper detection limit of the BAC II).

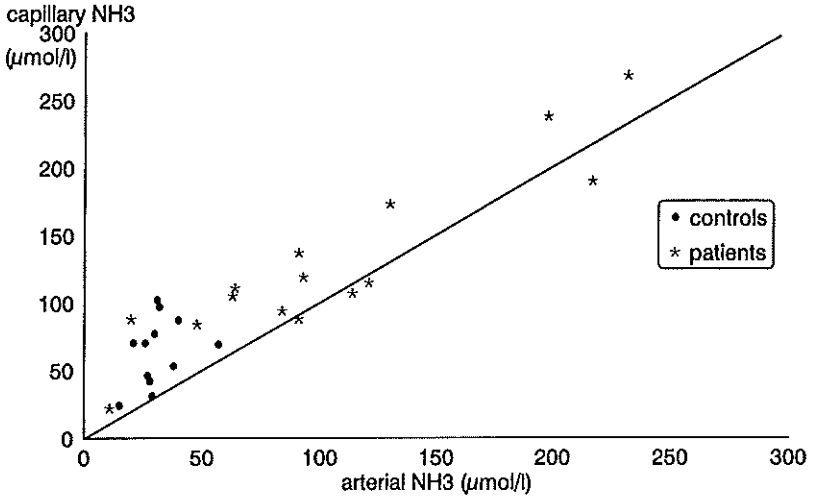

Figure 2: Capillary versus arterial ammonia measured with the BAC II in patients with cirrhosis of the liver and controls.

The capillary blood ammonia levels in 14 healthy controls during 3 consecutive days are shown in Table 2. The difference in ammonia level ranged from 0 to 84 µmol (median value 19 µmol) and the mean coefficient of variation was 29.6 %.

Table 2: Day-to-day variation of capillary ammonia (μmol/l) measured with the BAC II in healthy controls.

Controls	day 1	day 2	day 3	mean	CV, %*
1	99	83	72	85	16.0
2	53	74	23	50	51.2
3	76	133	88	99	30.4
4	101	58	75	78	27.8
5	41	56	35	44	24.6
6	45	34	118	66	69.5
7	36	57	35	43	29.1
8	45	57	35	46	24.1
9	53	53	76	61	21.9
10	36	37	64	46	34.8
11	69	39	32	47	42.1
12	37	51	60	49	23.5
13	56	62	61	60	5.4
14	41	53	52	49	13.7

* coefficient of variation

DISCUSSION

The ammonia determination in arterial blood reflects the severity of hepatic encephalopathy better than that in venous blood.[1] However, in contrast to arterial blood gas studies, there is much resistance to perform arterial punctures to measure ammonia in patients with liver disease. Capillary levels have been suggested to correspond closely to arterial levels and could be an acceptable alternative.[7] Peltola et al[8] performed a study in which capillary and venous ammonia levels were compared using the BAC II. The ammonia concentration in capillary blood was considerably higher than that in venous blood and sweat was considered as the contaminating source. However, it is not clear from the text if measures were taken to prevent this contamination. Huizenga et al[9] found that capillary ammonia levels were not statistically significant from arterial ammonia levels after thorough cleansing of the fingertip with chorhexidin before puncture.

We performed a study to determine whether capillary ammonia levels measured with the BAC II, after thoroughly washing the hands and cleansing the fingertip with chlorhexidin in 70 % alcohol, agree with arterial ammonia levels and are reliable in monitoring patients with liver disease. Three Dutch centers participated in this pilot study and found similar results. The data showed a correlation ($r = 0.92$) between capillary and arterial ammonia in a patient and a control group, however, agreement was poor as the capillary ammonia levels were considerably higher than the arterial ammonia levels. Both in the control and patient group the differences between capillary and arterial ammonia levels were statistically significant. Furthermore, capillary ammonia measurements during 3 consecutive days in 14 healthy controls showed poor

reproducibility. Interpretation of these data would have been easier if serial arterial ammonia levels in the controls were available, but this was not possible due to medical ethical reasons. However, the results showed such a marked variation indicating that the reproducibility of capillary ammonia levels is probably low.

The finding that the capillary ammonia concentration was lower than the arterial ammonia concentration in 4 patients (Fig. 2), lead us to the conclusion that this might have been venous capillary blood, as venous ammonia levels are lower than arterial ammonia levels in cirrhotics.[1] Capillary values could have corresponded better to arterial values if capillary blood had been arterialized by holding the hands in a bath of warm water during 10 minutes. However, this needs further investigation.

We conclude that, using the described cleansing and puncture procedure, capillary ammonia measurements with the BAC II are unreliable for monitoring patients with hyperammonemic diseases. Our experience suggests that ammonia should be measured from arterial blood.

Acknowledgements:

This study was performed with a grant from Solvay Pharma B.V..

REFERENCES

1. Stahl J. Studies of the blood ammonia in liver disease: its diagnostic, prognostic and therapeutic significance. Ann Intern Med 1963; 58: 1-24.
2. Huizenga JR, Tangerman A, Vos JGJ, Gips CH. Bepaling van ammoniak in bloed met de nieuwe Blood Ammonia Checker II systeem (BAC II). Tijdschr NVKC 1992; 17: 224-226.
3. Huizenga JR, Tangerman A, Gips CH. A rapid method for ammonia determination using the new Blood Ammonia Checker (BAC) II. Clin Chim Acta 1992; 210: 153-155.
4. Conn HO. Finally! Automated microanalysis of ammonia in arterial blood. Clin Chim Acta 1992: 210: 1-3.
5. Ypma ST, Blijenberg BG, Leijnse B. Evaluation of the Dupont aca ammonia procedure. Clin Chem 1978: 24: 489-492.
6. Brusilow SW, Gordes EH. Ammonia secretion in sweat. Am J Physiol 1968; 214: 513-517.
7. McCullough H. A simple microtechnique for the determination of blood ammonia and a note on the effect of exercise. Clin Chim Acta 1969; 9: 101-105.
8. Peltola O, Näntö V, Joronen I, Parto K, Simell O. Measurement of ammonia from skin-puncture blood samples: erroneously high values due to contamination with sweat, paper presented at the IX European Congress of Clinical Chemistry, Cracow, 1991.
9. Huizenga JR, Gips CH. Determination of blood ammonia using the ammonia checker. Ann Clin Biochem 1983; 20: 187-189.

Chapter 3

THE DIAGNOSIS OF SUBCLINICAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS USING NEUROPSYCHOLOGICAL TESTS AND AUTOMATED ELECTROENCEPHALOGRAM ANALYIS

The contents of this chapter have been published in:
Hepatology (1996, 24: 556-560) under the same title with the following authors:
J.C. Quero, I.J.C. Hartmann, J. Meulstee, W.C.J. Hop, S.W. Schalm.

ABSTRACT

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 2 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 testmethod 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.

INTRODUCTION

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 descibed, 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 neurophysiologial 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.

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. auto-immune, 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 orientated 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 $\pm$ 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 a 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 5kΩ. After applying the usual bandpass filters (0.53 - 35 Hz) 2 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 (MDF), 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 21 - 75). A θ activity above the 97.5th percentile (i.e., approximately the mean plus 2 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[37] (Dimension SMS) (Dupont de Nemours; Wilmington, DE) 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 $p = 0.05$.

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] 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.

Table 1: Prevalence of abnormal psychometric tests and abnormal spectral EEG in 137 cirrhotic patients without clinical hepatic encephalopathy.

Diagnostic test	n° tested	n° abnormal	% abnormal
NCT-A (corrected for age)	137	9	7
Symbol Digit Test	136	7	5
$\geq$ 1 abnormal psychometric test	137	14	10
spectral EEG	137	23	17

The agreement between the outcomes of the psychometric tests and spectral EEG was poor (K = 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 = 0.03 and 0.01, 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.

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	Observed agreement: (107+2)/137 = 0.80
					Kappa: 0.03
		114	23	137	
SDT	normal	111	19	130	
	abnormal	3	4	14	Observed agreement: (111+4)/137 = 0.84
					Kappa: 0.20
		114	23	137	
NCT *and* SDT	normal	105	18	123	
NCT *or* SDT	abnormal	9	5	14	Observed agreement: (105+5)/137 = 0.80
					Kappa: 0.16
		114	23	137	

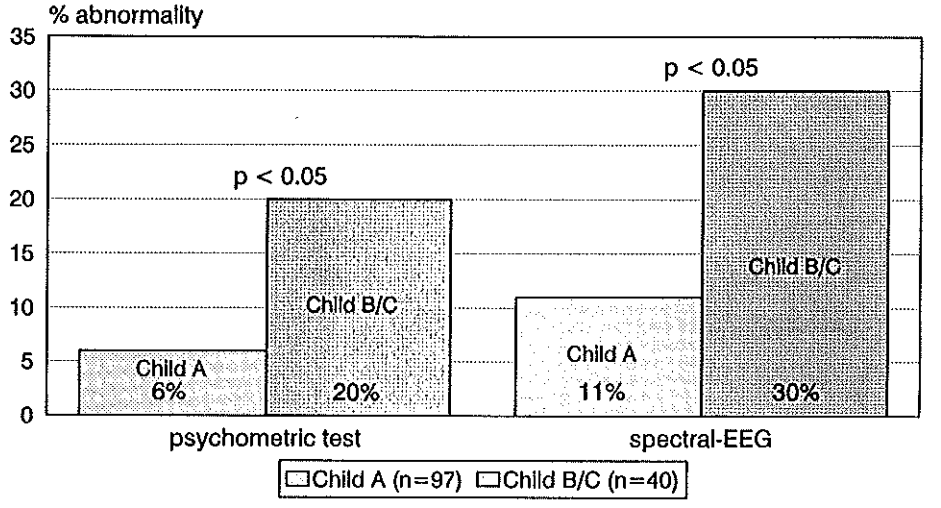

Figure 1: Percentage of abnormal test results in cirrhotic patients with a good liver function (Child-Pugh grade A, n=97) and cirrhotic patients with a diminished liver function (Child-Pugh grade B or C, n=40)

Table 3 Clinical and laboratory characteristics of the cirrhotic patients with normal and abnormal psychometric tests (3a) and spectral-EEG (3b).

3a	normal NCT and SDT	abnormal NCT or SDT	p value
patient number	123	14	
♂♂ : ♀♀	88 : 35	11 : 3	0.8
age (years)	48.1 ± 14	58.1 ± 11	< 0.05
arterial NH_3 (μmol/l)	54.3 ± 33	70.2 ± 30	0.12
Child-Pugh B or C	26%	47%	< 0.05
alcohol as etiology	21%	36%	0.31

3b	normal EEG	abnormal EEG	p value
patient number	114	23	
♂♂ : ♀♀	81 : 33	18 : 5	0.6
age (years)	47.2 ± 14	58.5 ± 11	< 0.01
arterial NH_3 (μmol/l)	51.4 ± 32	75.1 ± 26	< 0.001
Child-Pugh B or C	25%	52%	< 0.05
alcohol as etiology	19%	39%	< 0.05

In patients with alcoholic cirrhosis, a higher prevalence of abnormal tests was found compared to 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 liverdisease, 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, $p < 0.01$). 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, 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).

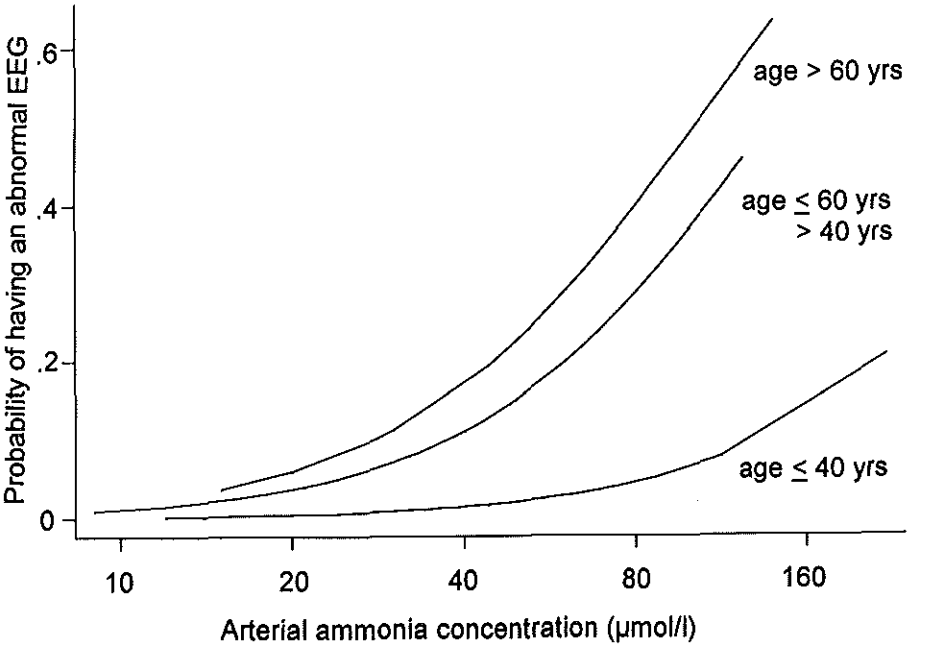

Figure 2: Probability of having an abnormal spectral EEG in different patient age groups according to the arterial ammonia concentration.
(Note: logarithmically transformed horizontal axis)

Table 4 Multivariate analysis of the probability of abnormal test results. Odds-ratios are given for an abnormal EEG and for at least one abnormal psychometric tests (Odd-ratios of 1 indicate no association).

		abnormal spectral EEG		abnormal psychometric test	
		Odds-ratio	p-value	Odds-ratio	p-value
Age		1.8[a]	0.01	1.8[a]	0.04
Ammonia		3.1[b]	0.01	1.2[b]	0.74
Child-Pugh	A[#]	1	-	1	-
	B/C	1.1	0.94	2.4	0.26
Alcoholic	No[#]	1	-	1	-
	Yes	1.7	0.36	1.6	0.48

(a) as compared to 10 years younger
(b) as compared to a 50% lower NH3
(#) reference category

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 (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 labourers, who are not familiar with the English alphabet. To document this, we administered the NCT part B 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. However, this result must be interpreted with caution because 33% of the Dutch speaking foreigners scored abnormal in the NCT part B in contrast to 11% of the native Dutch patients (data not shown). The percentage of abnormality in the NCT part B 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 can not 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, 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).

Acknowledgements:

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 for their expert technical assistance.

REFERENCES

1. Butterworth RF. Pathogenesis and treatment of Portal-Systemic Encephalopathy: An Update. Dig Dis Sci 1992; 37: 321-327.
2. Parsons-Smith BG, Summerskill WHJ, Dawson AM, Sherlock S. The electroencephalopgraph in liver disease. Lancet 1957; 2: 867-871.
3. Zeegen R, Drinkwater JE, Dawson AM. Method for measuring cerebral dysfunction in patients with liver disease. Br Med J 1970; 2: 633-636.
4. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 1978; 75: 462-469.
5. Gilberstadt SJ, Gilberstadt H, Zieve L, Buegel B, Collier RO, McClain CJ. Psychomotor performance defects in cirrhotic patients without overt encephalopathy. Arch Intern Med 1980; 140: 519-521.
6. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Döll W. Latent portasystemic encepalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981; 26: 622-630.
7. Marchesini G, Zoli M, Dondi C, Cecchini L, Angiolini A, Bianchi FB, Pisi E. Prevalence of subclinical hepatic encephalopathy in cirrhotics and relationship to plasma amino acid balance. Dig Dis Sci 1980; 25: 763-768.
8. Loguercio C, Del Vechio-Blanco C, Coltorti M. Psychometric tests and latent portal-systemic encephalopathy. Br J Clin Pract 1984; 38: 407-411.
9. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, non-shunted patients with cirrhosis. J Hepatol 1986; 3: 75-82.
10. Joelsson B, Aslund U, Hultberg B, Alwmark A, Gullstrand P, Bengmark S. Portal-systemic encephalopathy. Influence of shunt surgery and relations to serum amino acids. Scand J Gastroenterol 1986; 21: 900-906.
11. Moore JW, Dunk AA, Crawford JR, Deans H, Besson JAO, De Lacey G, Sinclair TS, Mowat NAG, Brunt PW. Neuropsychological deficits and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis. J Hepatol 1989; 9: 319-325.
12. Sood GK, Sarin SK, Mahaptra J, Broor SL. Comparative efficacy of psychometric tests in detection of subclinical hepatic encephalopathy in nonalcoholic cirrhotics: search for a rational

approach. Am J Gastroenterol 1989; 2: 156-159.

13. Schomerus H, Schreiegg J. Prevalence of latent portasystemic encephalopathy in an unselected population of patients with liver cirrhosis in general practice. Z Gastroenterol 1993; 31: 231-234.
14. Tarter RE, Hegedus AM, van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. Gastroenterology 1984; 86: 1421-1427.
15. Yen CL, Liaw YF. Somatosensory evoked potentials and number connection test in the detection of subclinical hepatic encephalopathy. Hepatogastroenetrol 1990; 37: 332-334.
16. Gitlin N. Subclinical Portal-Systemic Encephalopathy. Am J Gastroenterol 1988; 82:8-11.
17. De Bruijn KM Blendis LM, Zilm DH Carlen PL, Anderson GH. Effect of dietary protein manipulations in subclinical portal-systemic encephalopathy. Gut 1983; 24: 53-60.
18. McClain CJ, Potter TJ, Kromhout JP, Zieve L. The effect of lactulose on psychomotor performance tests in alcoholic cirrhotics without overt hepatic encephalopathy. J Clin Gastroenterol1984; 6: 325-329.
19. Egberts EH, Schomerus H, Hamster W, Jürgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. Gastroenterology 1985; 88: 887-895.
20. Morgan MY, Alonso M, Stanger LC. Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. J Hepatol 1989; 8: 208-217.
21. Conn HO. Trailmaking and number-connection tests in the assessment of mental state in portal systemic encephalopathy. Am J Dig Dis 1977; 22: 541-550.
22. Koch H, Schauder P, Schäfer G, Dahme B, Ebel W, Vahldiek B, König F, Henning H, Untersuchungen zur diagnose und prävalenz der latenten hepatischen encephalopathie. Z Gastroenterol 1990; 28: 610-615.
23. Davies ADM. The influence of age on Trail Making Test performance. J Clin Psychology 1968; 24: 96-98.
24. Zeneroli ML, Cioni G, Ventura P, Russo AM, Venturini I, Casalgrandi G, Ventura E. Interindividual variability of the number connection test. J Hepatol 1992; 15: 263-264.
25. Mehndirrata MM, Sood GK, Sarin SK, Gupta M. Comparative evaluation of visual, somatosensory, and auditory evoked potentials in the detction of subclinical hepatic encephalopathy in patients with nonalcoholic cirrhosis. Am J Gastroenterol 1990; 85: 799-803.
26. Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Künkel H.

Neurophysiological assessment of early hepatic encephalopathy. Electroenceph Clin Neurophysiol 1990; 75: 289-295.

27. Van der Rijt CCD, Schalm SW, de Groot GH, de Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph Clin Neurophysiol 1984; 57: 423-426.
28. Levy LJ, Bolton RP, Losowsky MS. The use of the visual evoked potential (VEP) in delineating a state of subclinical hepatic encephalopathy. A comparison with the number connection test. J Hepatol 1987; 5: 211-217.
29. Johansson U, Andersson T, Persson A, Eriksson LS. Visual evoked potential - a tool in the diagnosis of hepatic encephalopathy? J Hepatol 1989; 9: 227-233.
30. Hamster W, Kluck M, Schomerus H. PSE-Syndrom-Test. Kurzform. Beltz Test Gesellschaft, Weinheim. 1985.
31. Lezak MD. A compendium of tests and assessment techniques. In: Lezak MD. Neuropsychological assessment. Oxford university press, 1983
32. Reitan RM. Validity of the trail making test as an indication of organic brain damage. Percept Mot Skills 1958; 8: 271-276.
33. Schönleber R. Standardisierung eines psychometrischen Tests zur Erfassung der hepatischen Encephalopathie. Thesis. Tübingen 1989.
34. Stinissen J, Willems PJ, Coetsier P, Hulsman WLL. Handleiding bij de Nederlandstalige bewerking van de Wechsler Adult Intelligence Scale. Swets & Zeitlinger B.V., Lisse, The Netherlands 1970. ISBN 90 265 0208087.
35. Jasper HH. The ten twenty electrode system of the international federation. Electroenceph Clin Neurophysiol 1958; 10: 371-375.
36. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
37. Ypma ST, Blijenberg BG, Lijense B. Evaluation of the Dupont aca ammonia procedure. Clin Chem 1978; 24: 489-492.
38. Huizenga JR, Tangerman A, Gips CH. A rapid method for ammonia determination using the new Blood Ammonia Checker (BAC)II. Clin Chim Acta 1992; 210: 1-3.
39. Cox DR. Analysis of binary data. London: Methuen, 1970.
40. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic

encephalopathy. A double blind controlled trial. Gastroenterology 1977; 72: 573-583.

41. Conn HO. Subclinical hepatic encephalopathy. In: Hepatic encephalopathy: Syndromes and Therapies. Conn HO, Bircher J eds. Bloomington, Illinois: Medi-Ed Press, 1994: 27-39.
42. Pérez-Cuadrado Martínez E, Silva González C, Robles Reyes A. Variabilidad y alargamiento del tiempo de reacción en el diagnóstico precoz de la encefalopatía hepática subclínica. Rev Esp Enf Digest 1990; 77:29-32.
43. Tarter RE, Sandford SL, Hays AL, Carra JP. Hepatic injury correlates with neuropsychologic impairment. Intern J Neuroscience 1989; 44: 75-82.
44. Conn HO. Quantifying the severity of hepatic encephalopathy. In: Conn HO, Bircher J, eds. Hepatic encephalopathy: syndromes and therapies. Bloomington, Illinois: Medi-Ed Press, 1994; 13-26
45. Dustman RE, Shearer DE. EEG and event-related potentials in normal aging. Prog Neurobiol 1993; 41: 369-401.
46. Dierks T, Ihl R, Maurer K. Age-related changes of spontaneous EEG described by equivalent dipoles. Int J Psychophysiol 1993; 15: 255-261.
47. Duffy FH, McAnulty GB, Albert MS. The pattern of age-related differences in electrophysiological activity of healthy males and females. Neurobiol Aging 1993; 14: 73-84.
48. Hartikainen P, Soininen H, Partanen J, Helkala EL, Riekkinen P. Aging and spectral analysis of EEG in normal subjects: a link to memory and CSF AChE. Acta Neurologica Scandinavica 1992; 86: 148-155.
49. Oken BS, Kaye JA. Electrophysiologic function in the healthy, extremely old. Neurology 1992; 42: 519-526.

Chapter 4

DOES SUBCLINICAL HEPATIC ENCEPHALOPATHY AFFECT DAILY FUNCTIONING?

The contents of this chapter have been submitted for publication under the same title with the following authors: J.C. Quero, I. De Bruijn, I.J.C. Hartmann, M.L. Essink-Bot, W.C.J. Hop, S.W. Schalm

ABSTRACT

Subclinical hepatic encephalopathy (SHE) is assumed to have a negative effect on patients' daily functioning, therefore treatment is recommended. However, no studies have been performed that document the clinical relevance of SHE. We performed a study in which the prevalence of SHE was determined in 100 outpatients with liver cirrhosis using three psychometric tests (Number Connection Tests part A and B, and the Symbol Digit Test) and automated EEG analysis. In addition, the influence of chronic liver disease on patients' daily functioning was assessed using the Sickness Impact Profile (SIP) questionnaire. The distribution of SIP scores of the patients with liver cirrhosis differed from the reference scores of the general population. Patients (n=32) with SHE had a worse SIP score (median score 8.3) than those (n=68) without SHE (median score 5) ($p < 0.01$). Multivariate analysis taking also into account age and severity of liver disease, showed that SHE independently was related to a diminished SIP score. The reproducibility of the SIP was high when the test was repeated after a 3-month period. We conclude that SHE implies impaired daily functioning and warrants attempt to treatment. Since not all patients with SHE had objective evidence of impaired daily functioning, routine treatment of SHE might not be justified.

INTRODUCTION

Clinical manifestations of hepatic encephalopathy (HE) include a decreased intellectual function, personality disorders, an altered level of consciousness and neuromuscular dysfunction.[1] In addition to clinical manifest HE,[2] a subclinical stage has been described, which cannot be detected through global clinical examination, but requires specific neuropsychological and neurophysiological examination.[3-11] The prevalence of subclinical hepatic encephalopathy (SHE) is estimated to vary from 23% to 41% according to recent studies using appropiate methods.[12-14] This variation in reported prevalence depends on the kind (psychometric or electrophysiologic) and number of tests used, and the population (etiology and severity of the liver disease) tested.

SHE is considered to be clinically relevant for 2 reasons. Firstly, it could be a preceding stage of clinical manifest HE.[3] However, this assumption is not proven as only one follow-up study[15] supports this concept. Secondly, the psychomotor deficits found in SHE could have a disadvanting influence on patients' daily functioning, for example in driving a car or at work.[16] In view of the reported high prevalence of SHE and its negative effect on daily life, routine screening of cirrhotic patients for SHE, and treatment of SHE is recommended.[17-19] However, the need of treatment of SHE is questionnable, as a recent study has shown that patients with SHE did not perform worse driving 'on the road' than patients without SHE.[20] Driving a car is an important, but small part of the total spectrum of daily activities. Therefore, on the basis of this study, no conclusions can be made about the effect of SHE on other aspects of daily functioning.

The influence of chronic diseases on daily life can be assessed using 'Health-related Quality of life' questionnaires.[21] The 'Sickness Impact Profile' (SIP) questionnaire, [22,23] is such an instrument for overall health assessment and has been used before to determine the influence of chronic liver disease on patients' daily functioning.[24-27]

The aim of the present study was to determine the prevalence of neuropsychological and neurophysiological defects in stable cirrhotic patients attending an university hospital outpatient clinic using a small neuropsychologic testbattery of three tests and the neurophysiological method of automated EEG analysis. The SIP questionnaire was used to determine the influence of SHE on daily functioning. In addition, the reproducibility of the SIP in cirrhotic patients was determined.

PATIENTS AND METHODS

Subjects

From January 1, 1992 to March 1, 1995, 100 consecutive patients with histologically proven cirrhosis (n=99) and/or a surgical portosystemic shunt (n=3) attending the (out)patient clinic of Internal Medicine II and Hepatogastroenterology of the University Hospital Rotterdam-Dijkzigt were enrolled in the study. Exclusion criteria were clinical manifest HE, history of recent (less than 6 weeks) alcohol abuse, use of benzodiazepines and/or anti-epileptics, inability to perform the psychometric tests and complete the SIP questionnaire due to insufficient knowledge of the Dutch language (e.g. foreign

labourers), and inability to perform the psychometric tests due to e.g. neurologic diseases or bad vision. All patients underwent a clinical and laboratory investigation, psychometric tests, and automated EEG analysis. In addition, the SIP questionnaire was administered. All examinations took place on the same day. Test-retest reliability of the SIP was assessed by re-administering the questionnaire to patients without signs of decompensated liver disease (i.e. jaundice, ascites, encephalopathy, or variceal bleeding) after a 3-month period.

Clinical and laboratory assessment

Mental state assessment included state of awareness; "Is the patient perfectly alert and well orientated 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. The Child-Pugh score was used to assess the severity of liver disease.[28] Three biochemical variables (serum albumin, bilirubin, and prothrombin time) in addition to the two clinical characteristics (presence or absence of ascites and encephalopathy) determine the Child-Pugh score. Each variable is given one to three points, leading to scores ranging from 5 (excellent liver function) to 15 points (poor liver function).

Neuropsychological assesment

Number Connection Test part A and B

These tests are derivatives from the Trail Making Test[29] and measure cognitive motor abilities. In the NCT part A patients have to connect numbers printed on paper consecutively from 1 to 25. Age dependent normal values of this NCT-A[30] have been developed in 681 persons without liver disease.[31] Normal values are expressed as the mean $\pm$ 2 standard deviations. In the NCT part B patients have to connect numbers from 1 to 13 and letters from A to L in alternating numerical and alphabetical order, eg. 1-A-2-B-3-C etc, requiring them to deal with 2 dimensions simultaneously. Age dependent normal values of this NCT-B have been developed in 237 healthy volunteers.[32] After explanation, abbreviated demonstration tests were administered to be sure the patient had understood it. Errors were not enumerated, but patients were instructed to return to the preceding correct number or letter 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.

Symbol Digit Test

This is a subtest of the Wechsler Adult Intelligence Scale (WAIS) and measures motor speed and accuracy.[33] 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. After explanation, an abbreviated demonstration test was administered to ensure that the patient understood the test correctly. The test score is the total number of correct sequential matchings of numbers to symbols in a 90-sec interval. A high score indicates a good performance. Data of 2169 Dutch and Belgian persons serve as a reference

group in the Netherlands.[34] A test result below the 2.5th percentile (i.e. the mean minus 2 standard deviations) is considered as abnormal.

Neurophysiological assessment

The EEG was recorded using standardized techniques 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 5kΩ. After applying the usual bandpass filters (0.53 - 35 Hz) 2 runs of 100 seconds each were recorded and compared for reproducibility. Artefact free recordings were selected and fed into a computer after AD 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 (MDF), and the relative powers of delta and theta activity. In a previous study[36] 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 21 - 75). A theta activity above 35% (i.e. the mean plus 2 standard deviations in controls) is considered abnormal

Assessment of daily functioning

The SIP questionnaire is an often used instrument that assesses the influence of disease and treatment on daily functioning.[22] The questionnaire consists of 136 items, which are grouped into twelve scales: sleep and rest, eating, work, home management, recreation and pastimes, ambulation,

mobility, body care and movement (scores of the latter three may be combined as a physical subscore) social interaction, alertness behavior, emotional behavior, communication (scores of the latter four may be combined as a psychosocial subscore). Apart from a 12-dimensional profile score and the physical and psychosocial scores, the SIP provides the opportunity to compute a total score. Each score ranges from 0 (best score) to 100 (worst score). Patients mark only items that relate to their health at that time. The SIP has been translated and validated for the Dutch population.[37, 38]

Statistical analysis

Wilcoxon's rank sum test or the Fisher Exact test were used to assess differences in clinical and laboratory characteristics between patients with and without SHE. Those variables reaching (borderline) statistical significance in the univariate analysis, were selected for multivariate analysis using multiple regression to determine their influence on patients' daily functioning. In this analysis SIP-scores were logarithmically transformed to reduce skewness of distributions. The limit for statistical significance was set at $p = 0.05$.

Test-retest reliability (reproducibility) was assessed using intra-class correlation coefficients. Values above 0.7 generally are considered to indicate good reliability.[39] Internal consistency reliability of the SIP scales was assessed using Cronbach's alpha.[40] The internal consistency of a multi-item scale is a measure of the homogeneity of the items. An alfa of 0.70 is considered to demonstrate good internal consistency.[41]

RESULTS

One hundred consecutive patients with cirrhosis and/or portosystemic shunting (61 male, 39 female, mean age 50.9 years, SD 13, range 15-74) were screened for SHE. The etiology of the cirrhosis was chronic viral hepatitis in 39 patients, alcohol abuse in 15 patients, and other causes (e.g. auto-immune, PBC, cryptogenic) in 46 patients. 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.).

Figure 1 shows that the mean SIP scores of our patient population with liver cirrhosis were higher than normal reference scores of the general population.[38]

Table 1 summarizes the prevalence of abnormality in age-corrected psychometric tests and automated EEG analysis found in our population.Thirtytwo patients had an abnormal automated EEG analysis (19 patients) and/or one or more abnormal psychometric tests (19 patients). These 32 patients were considered as having SHE, while the remaining 68 patients were considered not to have SHE. Clinical and laboratory characteristics of both patient groups are summarized in Table 2. The male/female ratio did not significantly differ between both groups. The same applied to the percentage of patients with alcohol abuse as etiology of the liver disease. There were significantly more patients with a Child-Pugh grade B or C in the patient group with SHE. In addition, there was a trend ($p=0.08$) towards a older age in the patients with SHE.

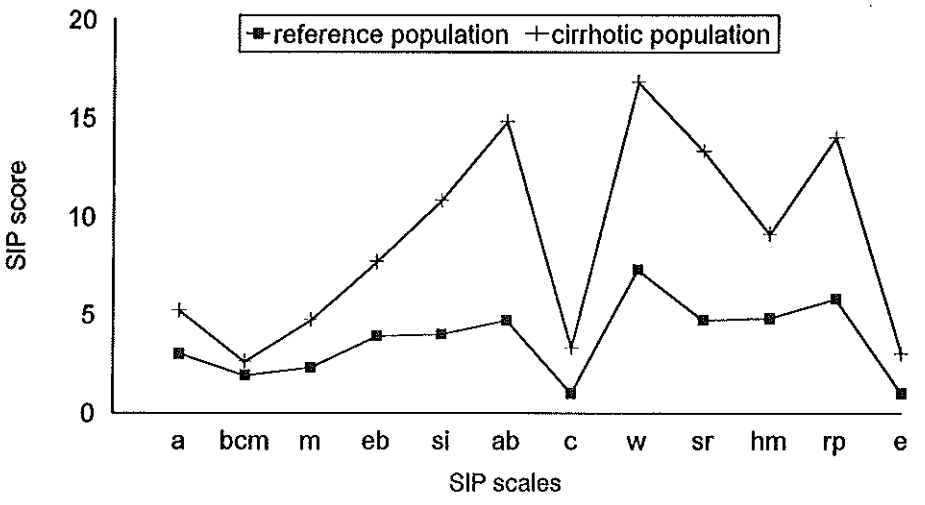

Figure 1: Mean SIP scale scores in 100 patients with liver cirrhosis and a reference group of 594 Dutch persons.[38]

Abbrevations: a (ambulation), bcm (bodycare and movement), m (mobility), eb (emotional behavior), si (social interactions), ab (alertness), c (communication), w (work), sr (sleep and rest), hm (home management), rp (recreation and pastimes), e (eating).

Table 1: Prevalence of abnormal neuropsychological and/or neurophysiological tests in 100 cirrhotic patients without clinical signs of hepatic encephalopathy.

	percentage abnormal
Number Connection Test A	5
Number Connection Test B	18
Symbol Digit Test	3
Automated EEG analysis	19

Table 2: Clinical and laboratory characteristics of cirrhotic patients with and without SHE.

	SHE - (n = 68)	SHE + (n = 32)	p value*
Male/female ratio	40:28	21:11	0.66
Age (years, median value + range)	51 (15-70)	55 (36-74)	0.08
Child Pugh grade A:B/C ratio	57:11	16:16	0.001
Alcohol/non-alcohol ratio	59:9	26:6	0.55

* Fisher Exact Test or Mann Whitney for age.

Functional impairment, defined as a total SIP score of at least 2.5[42], was found in 88 % of the patients with SHE compared to 71 % in patients without SHE (p=0.07).

Patients with SHE reported more impairment in several scales of the SIP than patients without SHE (Figure 2), reaching statistical significance only in the

'eating' scale and the total SIP score (Table 3).

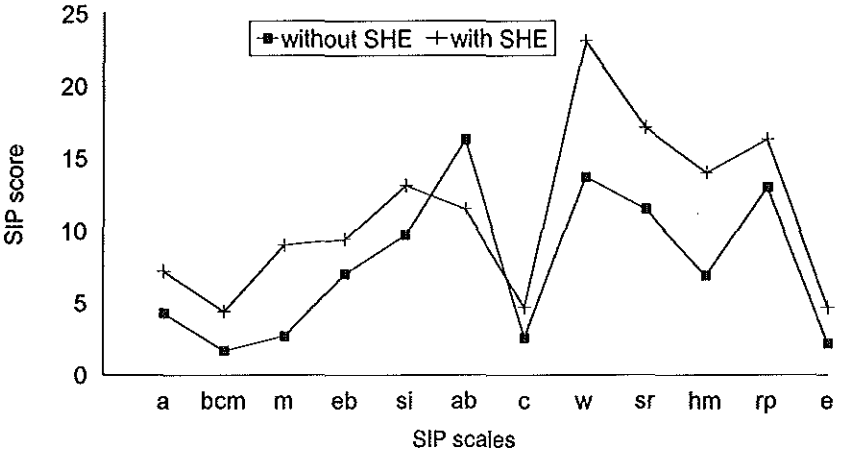

Figure 2: Mean SIP scale scores in 68 cirrhotic patients without SHE and 32 cirrhotic patients with SHE.

Abbrevations: as in figure 1

Table 3: SIP scores of cirrhotic patients with and without SHE. Scores are mininally 0 (good performance) and maximally 100 (bad performance).

	without SHE (n=68)	*with SHE (n=32)*	*p value**	*internal consistency#*	*nr. of items* per scale
Psychosocial scales					
Social Interactions	4.7 (0 - 58.4)	9.5 (0 - 41.3)	0.13	0.71	20
Alertness	8.2 (0 - 100)	4.1 (0 - 50.7)	0.89	0.85	10
Emotional Behavior	0 (0 - 77.6)	0 (0 - 39.6)	0.08	0.70	9
Communication	0 (0 - 40)	0 (0 - 45.9)	0.53	0.59	9
Total psychosocial subscore	4.6 (0 - 54.2)	7.4 (0 - 32.3)	0.24	0.91	
Physical scales					
Ambulation	0 (0 - 22)	4.2 (0 - 50.8)	0.22	0.48	12
Mobility	0 (0 - 28)	0 (0 - 65.6)	0.22	0.72	10
Bodycare and movement	0 (0 - 14.5)	0 (0 - 36.1)	0.28	0.74	23
Total physical subscore	0.4 (0 - 14.1)	1.6 (0 - 40.8)	0.15	0.87	
Independent scales					
Sleep/rest	11.8 (0 - 45.7)	12.2 (0 - 56.7)	0.12	0.40	7
Work	0 (0 - 46.1)	16.2 (0 - 46.1)	0.07	0.60	9
Home management	6.6 (0 - 31.6)	14.0 (0 - 75)	0.09	0.48	10
Recreation and pastimes	10.2 (0 - 53.6)	10.2 (0 - 73.5)	0.53	0.46	8
Eating	0 (0 - 18.7)	5.2 (0 - 19.7)	0.01	0.26	9
Total SIP score	5 (0 - 31.8)	8.3 (0 - 29.8)	0.01	0.92	137

Median scores are given, range between brackets. Statistics: *Wilcoxon's rank sum test, # Cronbachs α (pooled data)

Possible confounders in these findings could be age and the severity of liver disease, as patients with SHE tended to be older and had a more severe liver disease as compared to those without SHE (Table 2). Therefore, SHE, age and the Child-Pugh classification were selected for multivariate analysis to analyse their impact on the SIP. This analysis showed that both age and Child-Pugh classification, in addition to SHE, did not significantly affect the total SIP score.

The results of the SIP scores were similar between the various etiologies of the chronic liver disease. Patients with alcoholic cirrhosis and chronic viral hepatitis reported only more impairment on the physical subscore of the SIP as compared to non-viral and non-alcoholic cirrhotics (data not shown).

Reliability testing of the SIP questionnaire in our patient population using internal consistency measures showed that 7 subscales of the SIP fell below the recommended α-coefficient of 0.70 (Table 3). This suggests that the items of these SIP scales are not homogeneous in the population of patients with liver cirrhosis; i.e. the items of such a scale do not reliably represent an underlying characteristic.[43] The high internal consistency of the total SIP score is at least partly attributable to the high number of items.

The reproducibility of the SIP questionnaire was high as we found a good correlation between the SIP results in a 3-month interval (Table 4). Minor, statistically not significant, differences of median SIP scores were found between the first and second completed SIP questionnaire, indicating that during the 3 months patients had not systematically changed with regard to the SIP questionnaire.

Table 4: SIP scores of 38 cirrhotic patients at baseline and after 3 months.

	t = 0 months	*t = 3 months*	*p value**	*Intra-class correlation*
Psychosocial scales				
Social Interactions	7.4 (0 - 48.5)	5.9 (0 - 35.3)	0.82	0.84
Alertness	3.8 (0 - 66.5)	0 (0 - 74.5)	0.46	0.89
Emotional Behavior	0 (0 - 68.7)	0 (0 - 48.5)	0.77	0.81
Communication	0 (0 - 52.4)	0 (0 - 52.4)	0.87	0.82
Total psychosocial subscore	5.6 (0 - 44.3)	4.8 (0 - 42.7)	0.56	0.94
Physical scales				
Ambulation	0 (0 - 35.2)	0 (0 - 39.3)	0.69	0.88
Mobility	0 (0 - 46.6)	0 (0 - 34.6)	0.85	0.58
Bodycare and movement	0 (0 - 18.0)	0 (0 - 18.2)	0.99	0.88
Total physical subscore	1.3 (0 - 23.4)	1.8 (0 - 42.7)	1.0	0.89
Independent scales				
Sleep/rest	10.9 (0 - 73.5)	4.9 (0 - 56.7)	0.56	0.83
Work	13.3 (0 - 46.1)	10.5 (0 - 46.1)	0.67	0.89
Home management	6.6 (0 - 41.3)	6.6 (0 - 44.9)	0.53	0.67
Recreation and pastimes	4.3 (0 - 63.7)	8.2 (0 - 54.0)	0.88	0.67
Eating	0 (0 - 18.7)	0 (0 - 19.6)	0.25	0.58
Total SIP score	5. 5 (0 - 32.3)	5.6 (0 - 30.7)	0.68	0.96

Median scores are given, range between brackets. Statistics: *Wilcoxon's rank sum test

DISCUSSION

We performed a study to determine the influence of SHE on the Quality of Life. Three psychometric tests with age-specific normal values (NCT-A and B, SDT) and automated EEG analysis were selected to be used as a neuropsychological and neurophysiological screen for SHE. We defined SHE as at least one abnormal psychometric test and/or automated EEG analysis. Using this (arbitrary) definition we found a SHE prevalence of 32% in our outpatient cirrhotic population, which is in agreement with the prevalence found in studies using the same methods.[12-14]

The clinical relevance of SHE in our population was not obvious as these patients do not show mental or neurological abnormalities on clinical examination. Furthermore, according to the patients themselves and their spouses, the majority of these patients seemed to function well in their social environment and at work. We used the SIP as a method for evaluating the influence of SHE on daily functioning in cirrhotic patients as this questionnaire contains items which resemble the complaints seen in early stages of HE (Table 5). In addition, this questionnaire has been used in a previous study in patients with SHE.[10]

In our study we found a diminished level of functioning in patients with SHE. Interestingly, patients with SHE showed a trend towards significant impairment of those activities (e.g. work, home management) which are expected to be affected in cognitive disorders. Although age and severity of liver disease could have influenced the results, multivariate analysis showed that they did not significantly affect the total SIP score.

Table 5: Example of items of the Sickness Impact Profile which resemble conditions seen in patients with early stages of hepatic encephalopathy

Scale	Item
Sleep and rest	- I am sleeping or dozing most of the time - day and night
Emotional behavior	- I act nervous or restless
Bodycare and movement	- I have trouble getting shoes, socks, or stockings on
Home management	- I have difficulty doing handwork, e.g. turning faucets, using kitchen gadgets, sewing, carpentry
Mobility	- I am staying in bed most of the time
Social Interactions	- I am doing fewer social activities with groups of people
Ambulation	- I walk more slowly
Alertness	- I react slowly to things that are said or done
Communication	- I have trouble writing or typing
Work	- I do not do my job as carefully and accurately as usual
Recreation and pastimes	- I am doing more inactive pastimes in place of my other usual activities
Eating	- I am eating special or different food, e.g. soft food, bland diet, low-salt, low-fat, low-sugar

How reliable are our findings? Firstly, our study was performed in a sample of appropriate size (n=100), which makes the results of the SIP more adequate for statistical analysis. Secondly, SHE was diagnosed using a combination of psychometric and electrophysiological tests, which is in

accordance with the established definition of SHE (i.e., neuropsychologic and electrophysiologic defects in patients with no clinical signs of hepatic encephalopathy). Furthermore, we only used validated psychometric tests with age-adjusted normal values, thereby abolishing the diagnostic bias caused by aging on neuropsychological performance.[14] Thirdly, we used a validated test to evaluate daily functioning, with reference values for the Dutch population. In addition, we found a good test-retest reliability of the SIP in our patient population with liver cirrhosis.

How logical are our findings? Patients with hepatic encephalopathy grade 1 can complain about e.g. sleep disturbances, impaired calculation, shortened attention, mild personality changes and muscular incoordination.[44] Patients with SHE (in literature considered as a preclinical stage of hepatic encephalopathy) should therefore, although to a lesser extent, have similar complaints in daily life. Indeed, our results showed that patients with SHE complained more than patients without SHE in SIP scales such as sleep and rest, work, emotional behavior and home management (all borderline significant). The finding that patients with SHE differed significantly in the SIP categorie 'eating' than patients without SHE can be explained by the fact that patients with SHE had a more severe liver disease (Table 2), and therefore had more often a salt or protein restricted diet.

Should we treat patients with SHE because of the diminished level of daily functioning found in this study? Up to now, no intervention studies have been performed, in which functional status is used as an outcome of treatment efficacy in SHE. Treatment of SHE could be beneficial in patients with stable liver disease and impaired performance at work or daily life. We, therefore, strongly suggest the use of 'health-related quality of life questionnaires' in trials

with treatment specifically directed to SHE. In addition, due to the low internal consistency of several subscales of the SIP, other 'quality of life questionnaires' should be evaluated.

REFERENCES

1. Butterworth RF. Pathogenesis and treatment of Portal-Systemic Encephalopathy: An Update. Dig Dis Sci 1992; 37: 321-327.
2. Parsons-Smith BG, Summerskill WHJ, Dawson AM, Sherlock S. The electroencephalopgraph in liver disease. Lancet 1957; 2: 867-871.
3. Gitlin N. Subclinical Portal-Systemic Encephalopathy. Am J Gastroenterol 1988; 82: 8-11.
4. Zeegen R, Drinkwater JE, Dawson AM. Method for measuring cerebral dysfunction in patients with liver disease. Br Med J 1970; 2: 633-636.
5. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 1978; 75: 462-469.
6. Gilberstadt SJ, Gilberstadt H, Zieve L, Buegel B, Collier RO, McClain CJ. Psychomotor performance defects in cirrhotic patients without overt encephalopathy. Arch Intern Med 1980; 140: 519-521.
7. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy ambulant, non-shunted patients with cirrhosis. J Hepatol 1986; 3: 75-82.
8. Sood GK, Sarin SK, Mahaptra J, Broor SL. Comparative efficacy of psychometric tests in detection of subclinical hepatic encephalopathy in nonalcoholic cirrhotics: search for a rational approach. Am J Gastroenterol 1989; 2: 156-159.
9. Schomerus H, Schreiegg J. Prevalence of latent portasystemic encephalopathy in an unselected population of patients with liver cirrhosis in general practice. Z Gastroenterol 1993; 31: 231-234.
10. Tarter RE, Hegedus AM, van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. Gastroenterology 1984; 86: 1421-1427.
11. Moore JW, Dunk AA, Crawford JR, Deans H, Besson JAO, De Lacey G, Sinclair TS, Mowat NAG, Brunt PW. Neuropsychological deficits and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis. J Hepatol 1989; 9: 319-325.
12. Koch H, Schauder P, Schäfer G, Dahme B, Ebel W, Vahldiek B, König F, Henning H, Untersuchungen zur diagnose und prävalenz der latenten hepatischen encephalopathie. Z Gastroenterol 1990; 28: 610-615.

13. Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Künkel H. Neurophysiological assessment of early hepatic encephalopathy. Electroenceph Clin Neurophysiol 1990; 75: 289-295.
14. Quero JC, Hartmann IJC, Meulstee J, Hop WCJ, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. Hepatology 1996; 24: 556-560.
15. Yen CL, Liaw YF. Somatosensory evoked potentials and number connection test in the detection of subclinical hepatic encephalopathy. Hepatogastroenterol 1990; 37: 332-334.
16. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Döll W. Latent portasystemic encepalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981; 26: 622-630.
17. McClain CJ, Potter TJ, Kromhout JP, Zieve L. The effect of lactulose on psychomotor performance tests in alcoholic cirrhotics without overt hepatic encephalopathy. J Clin Gastroenterol 1984; 6: 325-329.
18. Morgan MY, Alonso M, Stanger LC. Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. J Hepatol 1989; 8: 208-217.
19. Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double-blind placebo-controlled crossover study. Gastroenterology 1985; 88: 887-895.
20. Srivastava A, Mehta R, Rothke SP, Rademaker AW, Blei AT. Fitness to drive in patients with cirrhosis and portal-systemic shunting: a pilot study evaluating driving performance. J Hepatol 1994; 21: 1023-1028.
21. Kazis LE. Health outcome assessments in medicine: history, applications and new directions. Adv Intern Med 1991; 36: 109-130.
22. Bergner M, Bobbitt RA, Cartner WB, Gilson BS. The sickness impact profile: development and final revision of a health status measure. Med Care 1981; 19: 787-805.
23. Sullivan M. The Sickness Impact Profile (SIP): an instrument for overall health assessment; a basic evaluation. JDR 1988; 13: 167-169.
24. Tarter RE, Switala J, Arria A, Van Thiel DH. Impact of liver disease on daily living in transplantation candidates. J Clin Epidemiol 1991; 44: 1079-1083.
25. Tarter RE, Switala J, Arria A, Plail J, Van Thiel DH. Quality of life before and after orthotopic hepatic transplantation. Arch Intern Med 1991; 151: 1521-1526.

26. Tarter RE, Switala J, Plail J, Havrilla J, Van Thiel DH. Severity of hepatic encephalopathy before liver transplantation is associated with quality of life after transplantation. Arch Intern Med 1992; 152: 2097-2101.
27. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC, Perrillo RP, Carey W, Jacobson IM, Payne J, Dienstag JL, Van Thiel DH, Tamburro C, Martino FP, Sanghvi B, Albrecht JK. Assessing health-related quality of life in chronic hepatis C using the Sickness Impact Profile. Clinical Therapeutics 1994; 16: 334-343.
28. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
29. Reitan RM. Validity of the trail making test as an indication of organic brain damage. Percept Mot Skills 1958; 8: 271-276.
30. Hamster W, Kluck M, Schomerus H. PSE-Syndrom-Test. Kurzform. Beltz Test Gesellschaft, Weinheim. 1985.
31. Schönleber R. Standardisierung eines psychometrischen Tests zur Erfassung der hepatischen Encephalopathie. Thesis. Tübingen 1989.
32. Weissenborn K, Ruckert N, Hecker H. Interindividual variability and clinical use of the Number Connection Tests A and B. In: Capocaccia L, Merli M, Riggio O, eds. Advances in hepatic encephalopathy and metabolic nitrogen exchange. Boca Raton, Florida: CRC Press, 1995; 385-389.
33. Lezak MD. A compendium of tests and assessment techniques. In: Lezak MD. Neuropsychological assessment. Oxford university press, 1983
34. Stinissen J, Willems PJ, Coetsier P, Hulsman WLL. Handleiding bij de Nederlandstalige bewerking van de Wechsler Adult Intelligence Scale. Swets & Zeitlinger B.V., Lisse, The Netherlands 1970. ISBN 90 265 0208087.
35. Jasper HH. The ten twenty electrode system of the international federation. Electroenceph Clin Neurophysiol 1958; 10: 371-375.
36. Van Der Rijt CCD, Schalm SW, De Groot GH, De Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph Clin Neurophysiol 1984; 57: 423-426.
37. De Melker RA, Touw-Otten F, Jacobs HM, Luttik A. De waarde van de 'Sickness Impact Profile' als uitkomstmeting. Ned Tijdschr Geneeskd 1990; 134: 946-948.
38. Jacobs HM, Luttik A, Touw-Otten FWMM, De Melker RA. De 'Sickness Impact Profile':

resultaten van een valideringsonderzoek van de Nederlandse versie. Ned Tijdschr Geneeskd 1990; 134: 1950-1952.

39. Streiner DL, Norman GR. Health measurement scales. Oxford: Oxford Medical Publications, 1989 (ISBN 0 19 2617737)
40. Bravo G, Potvin L. Estimating the reliability of continuous measures with cronbach's alpha and intraclass correlation coefficient: toward the integration of two traditions. J Clin Epidemiol 1991; 44: 381-390.
41. Nunnaly JC. Psychometric theory. McGraw Hill, New York 1978.
42. Jacobs HM. Health status measurement in family medicine research. Thesis. Utrecht 1993.
43. Essink-Bot ML, Krabbe PFM, Agt HME van, Bonsel GJ. NHP or SIP? A comparative study in renal insufficiency associated anemia. Quality of Life Research 1996; 5: 91-100.
44. Conn HO. The hepatic encephalopathies. In: Conn HO, Bircher J, eds. Hepatic encephalopathy: syndromes and therapies. Bloomington. Medi-Ed press, 1994:1-12.

Chapter 5

DOES A LOW-DOSE OF LACTULOSE IMPROVE QUALITY OF LIFE IN PATIENTS WITH LIVER CIRRHOSIS?

The contents of this chapter are in press in:
Advances in hepatic encephalopathy and metabolic nitrogen exchange, Record CO (Ed), CRC Press Boca Raton, USA 1996 under the same title with the following authors: J.C. Quero, M. Groeneweg, J. Meulstee, W.C.J. Hop, S.W. Schalm

ABSTRACT

Treatment of subclinical hepatic encephalopathy (SHE) is recommended with the aim to improve daily functioning. However, no studies have been performed which document an improved quality of life after treatment. The aim of this study was to determine the efficacy of a low dose of lactulose (30 grams daily) on psychometric tests (NCT-A, SDT), spectral-EEG, and quality of life. A 6-months double-blind placebo controlled study was performed in 40 consecutive stable cirrhotic patients (29 male, mean age 51 years, 33 Child-Pugh grade A), who had elevated arterial ammonia levels at baseline. Quality of life was assessed using the Sickness Impact Profile (SIP) questionnaire. There were 4 drop-outs (2 in the lactulose group) during the treatment period (2 side effects, 1 progression into HE, 1 not associated with the trial medication). No significant changes were seen after treatment in the arterial NH_3, psychometric tests, EEG and total SIP score in both the lactulose and placebo group. We conclude that a low-dose lactulose treatment in cirrhotic patients is not effective with respect to ammonia, psychometric tests, EEG and quality of life. Whether patients with SHE and impaired quality of life will benefit from effective treatment (higher lactulose dose?) remains to be determined.

INTRODUCTION

Hepatic encephalopathy (HE) refers to neuropsychiatric abnormalities due to liver insufficiency. Traditionally, HE is clinically graded in four stages of severity ranging from abnormal behaviour to unresponsive coma.[1]

In addition to the clinical grading of HE, a subclinical stage has been described in which patients with cirrhosis, regardless of its etiology, demonstrate a number of quantifiable neuropsychological defects, yet have a normal mental and neurological status on global clinical examination.[2] Psychometric tests as well as neurophysiological tests can be used for diagnosing subclinical hepatic encephalopathy (SHE).[3] The prevalence of SHE has been reported to vary from 30%[4] to 84%.[5] The main reasons for such a wide variation in frequency are the lack of uniformity in the application of diagnostic tests, and the differences in the patient population.[6]

The perceptual-motor and visuopractic deficits found in SHE could have implications in performing routine activities (e.g. driving an automobile, doing manual tasks), especially in those patients working in mechanical and skilled occupations.[7-9]

Due to the high prevalence of SHE and its possible impact on daily life, treatment of SHE with ammonia lowering agents is recommended.[10] Intervention studies have been performed with non-absorbable disaccharides,[11-13] protein restriction,[14] and branched chain amino acids.[8, 15] In these intervention studies psychometric tests and EEG showed improvement after treatment, which suggests that SHE is reversible and of metabolic origin. However, it is unclear whether these treatment regimens also lead to an improved daily functioning.

The aim of this study was to determine whether a low dose of crystalline

lactulose improves neuropsychological and electrophysiological functioning in patients with liver cirrhosis. In addition, we wanted to assess whether this improvement would also result in an improvement of patients' daily functioning.

PATIENTS AND METHODS

Subjects

From October 1, 1992 to August 31, 1994, 40 consecutive biopsy-proven cirrhotic patients (29 male, mean age 50.8 years, SD 14, range 24-70, 33 Child-Pugh grade A, 6 grade B, 1 grade C) without any clinical signs of HE, and with elevated arterial ammonia levels attending the outpatient clinic of Internal Medicine II and Hepatogastroenterology of the University Hospital Rotterdam-Dijkzigt were entered into the study. The etiology of the cirrhosis was chronic viral hepatitis in 12 patients, alcohol abuse in 11 patients, and other causes (e.g. auto-immune, PBC, cryptogenic) in 17 patients. None of the patients received treatment for hepatic encephalopathy on entry into the study. Patients with clinical signs of HE, unstable liver disease, a history of recent alcohol abuse (less than 6 weeks), use of benzodiazepines and/or anti-epileptics were excluded from the study. On entry into the study, patients received a full examination, including a neurological examination, laboratory investigation, psychometric tests and spectral EEG. In addition, patients' daily functioning was assessed. All examinations were performed on the same day. At the onset of the trial, 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.). All patients had an elevated arterial ammonia level

(i.e., more than 30 μmol/l) at baseline measured with Dupont aca procedure.[16]

Neuropsychological assesment

Number Connection Test

This test is a derivative from the Trail Making Test[17] 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.

Symbol Digit Test

This is a subtest of the Wechsler Adult Intelligence Scale (WAIS) and measures motor speed and accuracy.[18] 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-sec interval. A high score indicates a good performance.

After explanation of each psychometric test, an abbreviated demonstration test was administered to ensure that the patient understood the test correctly.

Electrophysiological 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".[19] Electrode impedance was kept lower than 5kΩ. After applying the usual bandpass filters (0.53 - 35 Hz) 2 runs of 100 seconds each were recorded and compared for reproducibility. Artefact free recordings were selected and fed into a computer after AD 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 (MDF), and the relative powers of delta and theta activity.[20]

Assesment of daily functioning

The SIP questionnaire is an instrument that assesses the influence of disease and treatment on daily functioning.[21] The questionnaire consists of 136 items, which are grouped into twelve categories: sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement (scores of the latter 3 may be combined as a physical subscore) social interaction, alertness behavior, emotional behavior, communication (scores of the latter 4 may be combined as a psychosocial subscore). Apart the physical and psychosocial scores, the SIP provides the opportunity to compute a total score. Each score ranges from 0 (best score) to 100 (worst score). Patients mark only items that relate to their health at that time. The SIP has been translated and validated for the Dutch population.[22]

Study design

Patients were randomized consecutively to the lactulose or treatment group by a numbered randomization list supplied by the study sponsor after all entry data were completed. Crystalline lactulose sachets (containing 10 g crystalline lactulose) and matched placebo (containing lactose) sachets were kindly supplied by the study sponsor.

All patients started with a dose of 10 g lactulose/placebo daily, which was gradually increased to 10 g lactulose/placebo three times a day after one week. This dose was to be maintained until the end of the treatment period. In case diarrhoea occured, the daily dose was decreased by 10 g lactulose/placebo and maintained until the end of the treatment period. Patients were seen at monthly intervals to assess acceptability of treatment. In addition, arterial ammonia concentration, psychomotor performance, spectral EEG and patients' daily functioning was assessed at 3-monthly intervals. Lactulose/placebo was stopped after 24 weeks of treatment. Three months after treatment, a complete evaluation was performed in each patient, including arterial ammonia measurement, psychomotor performance, spectral EEG and daily functioning.

The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Written informed consent was obtained from all patiens in accordance with the EEC guidelines on Good Clinical Practice, which underwrites the principles of the Declaration of Helsinki, as most recently revised in Hong Kong, 1989.

Statistical analysis

To assess the similarity of the two groups at randomization, a number of clinical and laboratory characteristics were compared using the Chi^2 and

Wilcoxon's rank sum test. The main objective was to compare changes in the arterial ammonia concentration, spectral EEG, psychomotor performance and daily functioning at the end of treatment. Changes within treatment groups were evaluated using Wilcoxon's signed rank test. Wilcoxon's rank sum testing was performed to assess the difference in the graded response in the various parameters of SHE between both treatment groups. The limit for statistical significance was set at $p = 0.05$.

RESULTS

Patient characteristics at randomization are summarized in Table 1. Patients in the lactulose and placebo group appeared well matched for the major entry characteristics.

Table 1: Patient characteristics (mean ± standard deviation) on entry into the study

	lactulose group	placebo group
number of patients	19	21
age (years)	51.9 ± 13	49.7 ± 12
Male : female	14 : 5	15 : 6
Child Pugh A : B : C	14 : 4 : 1	19 : 2 : 0
arterial NH3 (μmol/l)	68.6 ± 24	68.1 ± 32
NCT (seconds)	30.3 ± 11	37.3 ± 13
SDT (points)	46.8 ± 13	45.8 ± 16
EEG: MDF	9.2 ± 1	8.8 ± 1
EEG: % theta	21.3 ± 16	28.9 ± 23

Forty patients with liver cirrhosis and an elevated arterial ammonia concentration entered the study. Four of the 40 patients entered into the trial did not complete the treatment period. Two patients (1 in the lactulose group, 1 in the placebo group) dropped out of the study due to development of diarrhoea; one patient (placebo group) due to development of HE and one patient (lactulose group) due to personal reasons not associated to the study. Of the remaining 36 patients who completed the treatment period, one patient died due to a gastrointestinal bleeding and one underwent a liver transplantation (both in the lactulose group) during the post-treatment survey period.

During treatment flatulence occured in 17 patients (8 patients in the lactulose group, 9 in the placebo group). Ten patients (5 patients in each treatment group) had severe diarrhoea; the lactulose dosage had to be lowered to 20 grams daily in 3 patients, and to 10 grams daily in 1 patient.

The effects of treatment are summarized in Tables 2 and 3 (per protocol analysis). Neither in the lactulose group, nor in the placebo group significant changes were found in the arterial ammonia levels, psychometric tests and spectral EEG after 24 weeks of treatment (Table 2). Also the changes in response in these parameters did not significantly differ between lactulose and placebo. A significant improvement in the NCT score was seen in the placebo group, but not in the lactulose group. However, the change in the NCT performance after treatment was not significantly different ($p = 0.22$) between lactulose and placebo, when adjusted for baseline values. Patients' daily functioning, as measured with the SIP, also did not change at the end of the treatment period (Table 3). A significant improvement in the lactulose as well as in the placebo group was seen in the psychosocial subscore of the SIP. However, the difference in the changes of the psychosocial subscore of the SIP

after treatment was not significant between the lactulose and placebo group. Similar results were obtained when intention to treat analysis was performed (data not shown).

Table 2: Biochemical, neuropsychological and electrophysiological parameters of SHE (mean ± standard deviation) of the patients who completed the study at baseline and at the end of the treatment (months).

	lactulose group		placebo group	
	t = 0	t = 6	t = 0	t = 6
NH_3 (μmol/l)	70.4 ± 24	69.2 ± 26	66.8 ± 33	70.8 ± 27
NCT (seconds)	29.2 ± 11	28.3 ± 11	37.4 ± 14	30.0 ± 8*
SDT (points)	46.7 ± 14	49.3 ± 19	46.2 ± 17	49.7 ± 19
EEG: MDF	9.2 ± 1.1	9.0 ± 1.5	8.8 ± 1.2	8.8. ± 1.0
EEG: % theta	21.6 ± 17	21.0 ± 16	28.8 ± 24	27.2 ± 23

* $p < 0.005$

Table 3: Social parameters of SHE (mean ± standard deviation) of the patients who completed the study at baseline and at the end of the treatment (months).

	lactulose group		placebo group	
	t = 0	t = 6	t = 0	t = 6
Psychosocial SIP score	13.8 ± 15	9.9 ± 13*	10.3 ± 12	9.0 ± 12#
Physical SIP score	2.9 ± 4	4.5 ± 5	2.5 ± 3	3.0 ± 4
Total SIP score	8.8 ± 9	7.9 ± 8	8.7 ± 7	8.0 ± 8

* $p < 0.05$, # $p < 0.01$

DISCUSSION

This study is among the first to study the effect of lactulose on the quality of life in patients with liver cirrhosis. Patients were treated for 6 months to assess acceptability of a chronic treatment for improving quality of life. Preselection of the patients was only made on the basis of an elevated arterial ammonia, as lowering of the ammonia concentration is a main objective in the treatment of HE.[23] In order to prevent side effects, we chose a low dose of lactulose. However, even with this low dose, 65% of the patients in the lactulose group experienced flatulence or diarrhoea; only one patient in this group had to be withdrawn from the study due to severe diarrhoea.

No effect of treatment was seen on the arterial ammonia concentration, psychometric tests, and spectral EEG. In the placebo group, NCT performance showed an improvement after 24 weeks, which could be explained by a learning-effect. In addition, treatment did not result in an improvement in patients' daily functioning as measured with the SIP.

Can we conclude from our results that treatment of SHE does not lead to an improved quality of life? There are several reasons why this conclusion can not be drawn from our results.

Firstly, the lactulose dose used by us could have been too low as no significant lowering of the arterial ammonia concentration was detected after 6 months of treatment. Secondly, no preselection was made on the basis of abnormal psychometric tests and spectral EEG. One could assume that improvement of the biochemical, neuropsychological, and electrophysiological markers of SHE is a prerequisite for improving quality of life in these patients. Whether cirrhotic patients with SHE will benefit from chronic lactulose

treatment remains to be determined. We, therefore, propose to perform future intervention studies with higher doses of lactulose, and only in patients with definite SHE and an impaired quality of life.

Acknowledgements:

This study was performed with a grant from Solvay Pharma B.V..

REFERENCES

1. Parsons-Smith BG, Summerskill WHJ, Dawson AM, Sherlock S. The electroencephalograph in liver disease. Lancet 1957; 2: 867-871.
2. Gitlin N. Subclinical portal-systemic encephalopathy. Am J Gastroenterol 1988; 83: 8-11.
3. Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Künkel H. Neurophysiological assessment of early hepatic encephalopathy. Egical defects and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis. J Hepatol 1989; 9: 319-325.
6. Quero JC, Schalm SW. Subclinical hepatic encephalopathy. Seminars in Liver Diseases 1996; 16: 241-248.
7. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Döll W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981; 26: 622-30.
8. Egberts EH, Schomerus H, Hamster W, Jürgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double-blind placebo-controlled crossover study. Gastroenterology 1985; 85: 887-95.
9. Kardel T, Lund Y, Zander Olsen P, Möllgaard V, Gammeltoft A. Encephalopathy and portocaval anastomosis. Scand J Gastroenterol 1970; 5: 681-685.
10. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, ambulant, non-shunted patients with cirrhosis. J Hepatol 1986; 3: 75-82.
11. Morgan MY, Alonso M, Stanger LC. Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. J Hepatol 1989; 8: 208-217.
12. McClain CJ, Potter TJ, Kromhout JP, Zieve L. The effect of lactulose on psychomotor performance tests in alcoholic cirrhotics without overt hepatic encephalopathy. J Clin Gastroenterol 1984; 6: 325-329.
13. Salerno F, Moser P, Maggi A, Vitaliani G, Benetti G. Effects of long-term administration of low-dose lactitol in patients with cirrhosis but without overt encephalopathy. J Hepatol 1994; 21:1092-1096.
14. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 1978; 75: 462-469.

15. Plauth M, Egberts EH, Hamster W, Török M, Müller PH, Brand O, Fürst P, Dölle W. Long-term treatment of latent portosystemic encephalopathy with branched-chain amino acids. A double-blind placebo-controlled crossover study. J Hepatol 1993; 17: 308-314.
16. Ypma ST, Blijenberg BG, Leijnse B. Evaluation of the Dupont aca ammonia procedure. Clin Chem 1978; 24: 489-492.
17. Reitan RM. Validity of the trail making test as an indication of organic brain damage. Percept Mot Skills 1958; 8: 271-276.
18. Lezak MD. A compendium of tests and assessment techniques. In: Lezak MD. Neuropsychological assessment. Oxford university press 1983.
19. Jasper HH. The ten twenty electrode system of the international federation. Electroenceph Clin Neurophysiol 1958; 10: 371-375.
20. Van Der Rijt CCD, Schalm SW, De Groot GH, De Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph Clin Neurophysiol 1984; 57: 423-426.
21. Bergner M, Bobitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: Development and final revision of a health status measurement. Medical Care 1981.; 19: 787-805.
22. Jacobs HM, Luttik A, Touw-Otten FWMM, Melker RA. The Sickness Impact Profile: validation of the Dutch version. Ned Tijdschr Geneeskd 1990; 134: 1950-1952.
23. Butterworth RF. Pathogenesis and treatment of Portal-Systemic Encephalopathy: An update. Dig Dis Sci 1992; 37: 321-327.

Chapter 6

THE EFFECT OF HELICOBACTER PYLORI ERADICATION ON THE ARTERIAL AMMONIA LEVELS IN PATIENTS WITH LIVER CIRRHOSIS

The contents of this chapter have been published in a short version in:
The Lancet (1995, 346: 713-714) under the title Hyperammonaemia and Helicobacter pylori with the following authors: J.C. Quero, I.J.C. Hartmann, F.W.M. de Rooij, J.H.P. Wilson, S.W. Schalm

ABSTRACT

Helicobacter pylori (H pylori) infection in patients with liver cirrhosis could be a risk factor for hepatic encephalopathy (HE), as H pylori produces large amounts of ammonia (NH_3) in the stomach. The aim of this study was to determine the effect of H pylori eradication on the blood ammonia level in patients with liver cirrhosis. In 63 consecutive biopsy-proven cirrhotic patients H pylori status was determined using the ^{14}C-urea breath test. In addition, fasting arterial NH_3 was determined.

Eleven patients with hyperammonaemia and H pylori infection were treated with omeprazole 40 mg daily and amoxycillin 500 mg four times daily for 2 weeks. Only one patient had not eradicated H pylori 2 months after treatment. H pylori eradication resulted in a significant reduction ($p < 0.05$) of baseline blood NH_3 levels from 79.3 μmol/l (SD 27, range 55-141) to 63.5 μmol/l (SD 27, range 27-121). Ten weeks after treatment the mean blood NH_3 level had risen to 78.7 μmol/l (SD 24, range 46-131), which was not significantly different from baseline values.

We conclude that H pylori eradication does not result in a long-term reduction of blood ammonia levels in hyperammonaemic patients with cirrhosis. Reduction of NH_3 after treatment can be explained by the non-specific effect of amoxycillin on ammonia-producing gut flora, rather than by the eradication of the ammonia-producing H pylori itself.

INTRODUCTION

Neurotoxic substances originating from the gut and bypassing the liver are believed to play a major role in the pathogenesis of hepatic encephalopathy. Some of the substances claimed to have a neurotoxic effect are ammonia, GABA, endogeneous benzodiazepines, tryptophane and glutamate.[1, 2] As none of these substances fully accounts for the development of HE, the pathogenesis of HE is believed to be multifactorial.[3] However, the ammonia hypothesis provides the strongest evidence as: 1) elevated arterial ammonia levels are frequently found in HE, 2) ammonia loading tests can cause HE in patients with cirrhosis of the liver or with a porto-caval shunt, 3) improvement of HE can be achieved with agents lowering the arterial ammonia level.[1]

Therapy of HE should focus on two aspects: amelioration of liver function, for instance by elimination of the etiologic factor, and secondly the therapy of HE itself. Until now the most effective therapy of HE is lowering of the blood ammonia by reducing the ammonia production of the colonic flora with either non-absorbable disaccharides, antibiotics or protein restriction.[4]

However, the colon is not the only part of the gastro-intestinal tract where ammonia is generated. Ammonia is also being produced in large quantities in the stomach of persons infected with Helicobacter pylori (H pylori).[5-7]

H pylori is a spiral-shaped bacterium, which is often found in the gastric mucosa of patients with antrum gastritis and/or duodenal ulcer and is believed to play a major role in the pathogenesis of these diseases.[8-12] The

assessment of the endogeneous urease activity of H pylori allows a simple and non-invasive detection of this micro-organism.[13-16]

As far as we know, no studies have been published with respect to the contribution of gastric ammonia production by H pylori to the total ammonia production in the gastro- intestinal tract. If this contribution is significant, H pylori-positive patients with liver cirrhosis could be at a higher risk of developing HE than H pylori-negative patients.[17-20] Recently, H pylori has indeed been named as a risk factor for HE.[21] Therefore, eradication of H pylori could be indicated for H pylori-positive patients with liver cirrhosis in order to treat or prevent episodes of HE. Several treatment regimes are being used for the eradication of H pylori.[22] A combination therapy of tripotassium dicitrato bismuthate (bismuth), amoxycillin and metronidazole is recommended, however, newer treatment regimes have proven efficacy with less side effects.[23-28]

The aim of the present study was to determine the effect of H pylori eradication on the arterial ammonia concentration in patients with liver cirrhosis.

PATIENTS AND METHODS

Subjects

From April 1, 1994 to May 31, 1995, 63 consecutive biopsy-proven cirrhotic patients (mean age 50 years, SD 14, range 18-70) attending the (out)patient clinic of Internal Medicine II and Hepatogastroenterology of the University Hospital Rotterdam - Dijkzigt were screened for the presence of

H pylori by a ^{14}C-urea breath test. In addition, the fasting arterial ammonia concentration was determined in each patient.

Subsequently, H pylori-positive patients with elevated arterial ammonia levels (defined as more than 50 μmol/l) received a combination therapy of omeprazole 40 mg daily and amoxycillin 500 mg four times daily for 2 weeks. Patients with unstable liver disease (i.e. over a period of 6 weeks prior to entry variations in medication and/or liver function tests (bilirubin, albumin, prothrombin time)) and those receiving treatment with lactulose or neomycin were excluded from this intervention study.

At the end of treatment fasting arterial ammonia level was determined. Ten weeks after the discontinuation of treatment patients received the final evaluation, consisting of a ^{14}C-urea breath test and a fasting arterial ammonia determination.

Laboratory assessments

Ammonia determination

Arterial blood was drawn in the morning in the fasting patient. A puncture was performed in the radial artery in the hyperextended wrist using a 2.0 ml heparinized syringe. After drawing blood the syringe was gently rotated and immediately placed on crushed ice. Ammonia measurements were performed within 15 minutes after puncture using the Dupont aca procedure (Dimension SMS) (Dupont de Nemours; Wilmington, DE).[29]

14C-urea breath test

The ^{14}C-urea breath test was performed in the morning in the fasting patient according to the method described by Rauws et al.[15] In summary, patients ingested a liquid test meal containing 110 kBq ^{14}C-urea. Breath samples were collected at baseline, and after 50 and 60 minutes. Patients were considered to be infected with H pylori when breath radioactivity was more than 0.07% of the administered ^{14}C dose/mmol expired CO_2 multiplied by bodyweight in kilograms.

Statistics

Wilcoxon's signed rank test was performed to assess the difference in arterial ammonia concentration before and after H pylori eradication therapy.

Ethics

This study was an investigator initiated study, and performed in accordance with the EEC guidelines on Good Clinical Practice, which underwrites the principles of the Declaration of Helsinki, as most recently revised in Hong Kong, 1989. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam - Dijkzigt. Patients were required to give their written informed consent before entering the study.

RESULTS

Thirtytwo (51%) out of 63 cirrhotic patients were infected with H pylori, as determined with the ^{14}C-urea breath test. Nineteen (59%) of these H pylori-infected patients had an elevated fasting arterial ammonia concentration, of which 13 patients entered the intervention study with omeprazole and amoxycillin. No side effects (diarrhoea, stomatitis, allergic exanthema) occured during the 2 weeks treatment.

Fasting arterial ammonia concentration decreased in the 13 patients from 87.0 μmol/l (SD 36, median 70, range 55-170) to 70.3 μmol/l (SD 30, median 65, range 27-124) after 2 weeks of treatment ($p=0.01$).

Two patients were withdrawn from the study in the posttreatment phase as they underwent a liver transplantation.

In only one of the 11 remaining evaluable patients treatment did not result in eradication of H pylori. The effect of therapy on the blood ammonia levels in the 10 patients who eradicated H pylori are shown in Figure 1. These 10 patients had a mean fasting arterial ammonia concentration of 79.3 μmol/l (SD 27, median 70, range 55-141) at baseline. After two weeks of treatment the mean fasting arterial ammonia concentration was reduced to 63.5 μmol/l (SD 27, median 62, range 27-121; $p=0.02$). Ten weeks after treatment the mean fasting arterial ammonia concentration in all patients had risen to 78.7 μmol/l (SD 18, median 82, range 46-107). This ammonia concentration did not differ significantly from baseline.

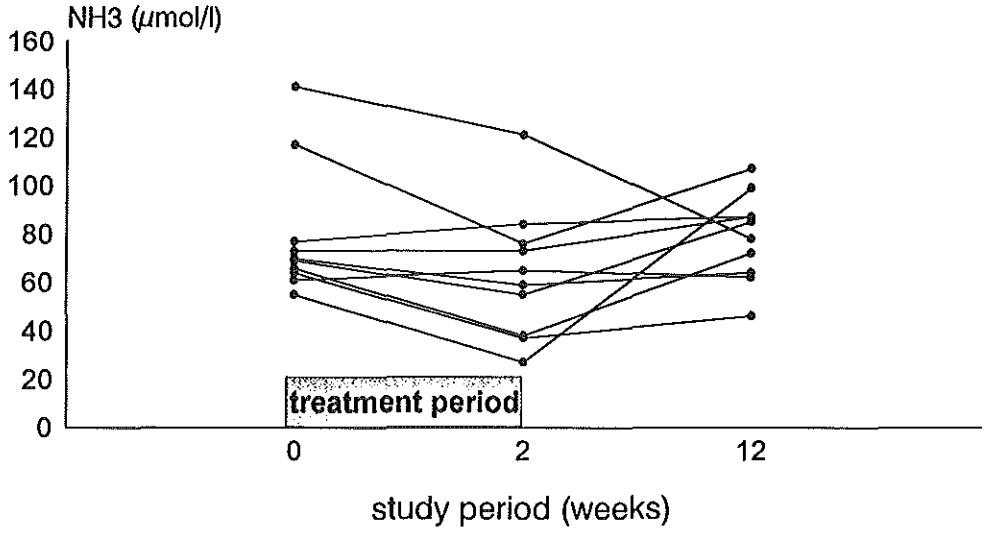

Figure 1: The effect of 2 weeks omeprazole 40 mg daily and amoxycillin 500 mg four times daily on the fasting arterial ammonia concentration in hyperammonaemic patients who eradicated Helicobacter pylori.

DISCUSSION

A possible role of gastric ammonia production in the pathogenesis of HE was already described in 1959.[17] Recently, the effect of eradication of H pylori on blood ammonia levels in 2 patients with HE has been described by Ito et al.[30] The authors suggested that the persistently lowered blood ammonia levels 5 months after therapy could only be explained by the absence of H pylori as the colonic flora should have been restored after this period. Prior to performing our study, we also experienced a remarkable improvement in one of our patients with HE after eradicating his H pylori infection with a combination therapy of metronidazole, bismuth and amoxycillin (the same antibiotics used in Ito's first patient). However, other mechanisms besides H pylori eradication might have been responsible for this effect.[31]

Our data confirm a fall in blood ammonia with eradication therapy of H pylori, but question whether this fall is due to eradication of ammonia-producing H pylori. The return of blood ammonia levels 2 months after therapy to baseline values in patients with eradication of H pylori suggests a non-specific effect of antibiotics rather than an effect of eradication of the organism. Our observations have been confirmed by Plevris et al,[32] who did not find a significant effect of H pylori on the blood ammonia level 2 hours after oral urea administration.

Acknowledgements:

This study was performed with a grant from Astra Pharmaceutica Nederland B.V..

REFERENCES

1. Butterworth RF. Pathogenesis and treatment of portal-systemic encephalopathy: an update. Dig Dis Sci 1992; 37: 321-327.
2. Record CO. Neurochemistry of hepatic encephalopathy. Gut 1991; 32: 1261-1263.
3. Schenker S, Brady CE. The pathogenesis of hepatic encephalopathy. In: Conn HO, Bircher J. Hepatic encephalopathy: management with lactulose and related carbohydrates. East Lansing, Michigan: Medi-Ed Press, 1988: 15-30.
4. Capocaccia L, Ferenci P, Fischer JE, Opolon P. Mechanisms of hepatic encephalopathy: certainties and uncertainties. Gastroenterology International 1989; 2: 131-140.
5. Mobley HLT, Cortesia LE, Rosenthal LE, Jones BD. Characterization of urease from Campylobacter pylori. J Clin Microbiol 1988; 26: 831-836
6. Triebling AT, Korsten MA, Dlugosz JW, Paronetto F, Lieber CS. Severity of Helicobacter-induced gastric injury correlates with gastric juice ammonia. Dig Dis Sci 1991; 38: 1089-1096.
7. Tsujii M, Kawano S, Tsuji, Fusamoto H, Kamada T, Sato N. Mechanism of gastric mucosal damage induced by ammonia. Gastroenterology 1992; 102: 1881-1888.
8. Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; 1: 1273.
9. Marshall B. Unidentified curved bacilli on gastric epithelium in chronic active gastritis. Lancet 1983; 1: 1273-1275.
10. Vaira D, Holton J, Barbara L. Helicobacter pylori and gastroduodenal disease. Gastroenterology International 1991; 4: 70-76.
11. Goodwin CS. Duodenal ulcers, campylobacter pylori, and the "leaking roof" concept. Lancet 1988; 2: 1467-1469.
12. Levi S, Haddad G, Ghosh P, Beardshal K, Playford R, Calam J. Campylobacter pylori and duodenal ulcers: the gastrin link. Lancet 1989; 1: 1167-1168.
13. Owen RJ, Martin SR, Borman P. Rapid urea hydrolysis by gastric Helicobacter. Lancet 1985; 1: 111.
14. Graham DY, Klein PD, Evans DJ, Evans DG, Alpert LC, Opekun AR, Boutton TW. Campylobacter pylori detected noninvasively by the 13C-urea breath test. Lancet 1987; 1: 1174-1177.

15. Rauws EAJ, Rayen EAV, Langenberg W, Waentel JV, Urji AA, Tytgat GN. 14C-urea breath test in Campylobacter gastritis. Gut 1989; 30: 789-803.

16. Graham DY, Klein PD, Evans DG, Evans DJ, Alpert LC, Opekun A, Jerdack GR, Morgan DR. Simple noninvasive method to test efficacy of drugs in the eradication of Helicobacter pylori infection: the example of combined bismuth subsalicylate and nitrofurantoin. Am J Gastroenterol 1991; 86: 1158-1162.

17. Lieber CS, Lefevre A. Ammonia as a source of gastric hypoacidity in patients with uremia. J Clin Invest 1959; 38: 1271-1277.

18. Nance FC, Kaufman HJ, Kine DG. Role of urea in the hyperammonemia of germ-free Eck fistula dogs. Gastroenterology 1974; 66: 108-112.

19. Hazell SL, Lee A. Campylobacter pyloridis, urease, hydrogen ion back diffusion, and gastric ulcers. Lancet 1986; 2: 15-17.

20. Marshall BJ, Langton SR. Urea hydrolysis in patients with campylobacter pyloridis infection. Lancet 1986; 1: 965-966.

21. Gubbins CP, Moritz TE, Marsano LS, Talwalkar R, McClain CJ, Mendenhall CL. Helicobacter pylori is a risk factor for hepatic encephalopathy in acute alcoholic hepatitis: the ammonia hypothesis revisited. Am J Gastroenterol 1993; 11: 1906-1910.

22. Heatley RV. The treatment of Helicobacter pylori infection. Aliment Pharmacol Ther 1992; 6: 291-303.

23. Rune S. Helicobacter pylori, peptic ulcer disease and inhibition of gastric acid secretion. Digestion 1992; 51: 11-16.

24. Unge P, Gad A, Gnarpe H, Olsson J. Does omeprazole improve antimicrobial therapy directed towards gastric Campylobacter pylori in patients with antral gastritis? Scand J Gastroenterol 1989; 24 (Suppl. 167): 49-54

25. Bell GD, Powell KU, Burridge SM, Pallecaros M, Jones PG, Gant PW, Harrison G, Trowell JE. Experience with 'triple' anti-Helicobacter pylori eradication therapy: side effects and the importance of testing the pre-treatment bacterial isolate metronidazole resistance. Aliment Pharmacol Ther 1992; 6: 427-435.

26. Bell GD, Powell KU, Burridge SM, Spencer G, Bolton G, Purse K, Brooks S, Prosser S, Harrison G, Gant PW, Jones PH, Trowell JE. Omeprazole plus antibiotic combinations for the eradication of metronidazole-resistant Helicobacter pylori. Aliment Pharmacol Ther 1992; 6: 751-758.

27. Labenz J, Gyenes E, Rühl GH, Börsch G. Two weeks treatment of with amoxicillin/omeprazole for eradication of Helicobacter pylori. Z Gastroenterol 1992; 30: 776-778.

28. Hosking SW, Ling TKW, Yung MY, Cheng A, Chung SCS, Leung JWC, Li AKC. Randomised controlled trial of short term treatment to eradicate Helicobacter pylori in patients with duodenal ulcer. Br Med J 1992; 305: 502-504.

29. Ypma ST, Blijenberg BG, Leijnse B. Evaluation of the Dupont aca ammonia procedure. Clin Chem 1978; 24: 489-492.

30. Ito S, Miyaji H, Azuma T, Li Y, Ito Y, Kato T, Kohli Y, Kuriyama M. Hyperammonaemia and Helicobacter pylori. Lancet 1995; 346: 125-125.

31. Morgan MH, Read AE, Speller PCE. Treatment of hepatic encephalopathy with metronidazole. Gut 1982; 23: 1-7.

32. Plevris JN, Morgenstern R, Hayes PC, Bouchier IAD. Hyperammoneamia in cirrhosis and Helicobacter pylori infection. Lancet 1995; 346: 1104.

Chapter 7

SUBCLINICAL HEPATIC ENCEPHALOPATHY: DIAGNOSIS, CLINICAL IMPLICATIONS, AND UPDATE ON INTERVENTION. A DISCUSSION

Subclinical hepatic encephalopathy (SHE) is a real, but rather mysterious entity for physicians, who deal with patients with liver cirrhosis.

The first problem a physician, who decides to screen patients for this entity, has to solve is which diagnostic methods he should use, as there is no "gold standard" diagnostic test.[1] The long list of diagnostic tests for the detection of SHE mentioned in the literature has caused this confusion.[2] Most authors propose the use of psychometric tests, because these are cheap, simple to perform, easy to interpret, and have a reported high sensitivity. However, the performance and interpretation of psychometric tests is not as simple as usually suggested.

Firstly, performance should be strictly standardized for proper intra- and interpatient comparison. Attention should always be paid to the lighting of the room, the vision of the patient (does he wear his reading glasses?), the sitting position, the materials used (appropriate pencil?), chronometry, and the scoring of the test.

Secondly, normal values should be available for each test. Even simple psychometric tests, such as the Number Connection Test part A (NCT-A), should be adjusted for age.[3] When a more complicated test, such as the Number Connection Test part B (NCT-B) that requires adequate knowledge of the alphabet, is selected, additional adjustment of normal values is required as its result is highly dependent on the education level of the patient.[4] In addition, normal values developed in one country should not be used in a patient population of another country. Furthermore, NCT forms supplied by a single company might be different.[5]

In summary, the use of a psychometric test in clinical practice requires the same attention to performance, normal values and quality control as is widely

accepted for biochemical tests.

Are psychometic tests, when correctly executed, alone sufficient for detecting SHE? Probably not, since overlap between abnormal psychometric test results and abnormal neurophysiological (EEG or evoked potentials) test results is poor.[4, 6] This observation suggests that these two different groups of test methods measure different components of cerebral impairment. Therefore, psychometric tests, as well as neurophysiological tests should both be used for the detection of SHE. The advantage of neurophysiological tests is that they are not influenced by age and educational background. Obvious disadvantages of these tests are the need for sophisticated, expensive equipment, and well-trained personnel. As in psychometric tests, standardization of the neurophysiological test performance is important. Carefull attention should be payed to the cooperation of the patient (required in visual and P300 evoked potentials) and to the wakefulness of the patient (required in spectral EEG). Probably the digestive state in which these tests are performed should also be standardized, as outcome may be affected by ingestion of a meal.[7]

Once the diagnostic tests have been performed, and a patient with SHE is identified, the physician is confronted with a second problem: What is the clinical significance of SHE?

The main characteristic of SHE is that practical abilities (i.e., functional performance) are impaired, while verbal abilities are maintained. This phenomenon has been explained by dividing human abilities in "crystallized" intelligence and "fluid" intelligence.[8] Crystallized intelligence plays a role in logical, and mathematical thinking. It consists of a whole set of ready solutions for known problems, which has been acquired during life-time through education. Fluid intelligence is the intelligence used for creative solutions in

unknown problems. It is important in nonverbal skills and perception of spatial relationships. Crystallized intelligence is rather stable, in contrast to fluid intelligence which is more unstable and firstly impaired in diffuse brain damage. These concepts are in accordance with the study of Kardel, who found that after a portocaval anastomosis patients performing intellectual tasks were less impaired in daily life than patients who worked with their hands.[9] The white collar worker will mainly use his crystallized intelligence and will, therefore, be not much impaired in his daily work. The blue collar worker, on the other hand, depends predominantly on his fluid intelligence for his daily work, and as a consequence will be more easily impaired. The clinical significance of SHE may, therefore, lie in restoring functional impairment in these patients.

The third problem, the physian has to deal with, is whether to treat a patient with SHE. Most physicians will be reluctant to treat an isolated abnormal diagnostic test in an asymptomatic patient. Automatic treatment of an abnormal neurophysiological or neuropsychological test is, therefore, not justified, especially since no effect of lactulose therapy could be observed in a double-blind trial in patients with cirrhosis and elevated blood ammonia levels.[10] Therapy appears desirable only for patients with functional impairment.[11, 12] No data are available which support prophylactic treatment of patients with SHE, although SHE is considered to precede the development of clinically overt HE. The recent introduction of the TIPS procedure in clinical hepatology provides an opportunity to study the course of SHE, and the effect of intervention.

In summary, the recognition of functional impairment is emerging as the key element in subclinical hepatic encephalopathy. In patients with diagnosed

SHE the physician should clearly ask for evidence of functional impairment. Quality of life asessment in such patients has documented diminished daily functioning independent of the severity of liver disease,[12] which strongly suggests a relationship between SHE and functional impairment. Progress in the area of SHE is to be expected if functional impairment related to SHE can be detected reliably in the individual patient in a simple way by the attending physician. Future research should be directed in the development and validation of such a diagnostic tool.

REFERENCES

1. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. The selection of diagnostic tests. In: Clinical epidemiology, a basic science for clinical medicine. Little, Brown and Company. USA 1991: 51-68.
2. Conn HO. Subclinical hepatic encephalopathy. In: Hepatic encephalopathy: Syndromes and Therapies. Conn HO, Bircher J eds. Bloomington, Illinois: Medi-Ed Press, 1994: 27-39.
3. Zeneroli ML, Cioni G, Ventura P, Russo AM, Venturini I, Casalgrandi G, Ventura E. Interindividual variability of the number connection test. J Hepatol 1992; 15: 263-264.
4. Quero JC, Hartmann IJC, Meulstee J, Hop WCJ, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. Hepatology 1996, 24: 556-560.
5. Quero JC, Schalm SW. Subclinical hepatic encehalopathy. Seminars in Liver Disease 1996; 16: 241-248.
6. Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Kunkel H. Neurophysiological assessment of early hepatic encephalopathy. Electroencep Clin Neurophysiol 1990; 75: 289-295.
7. Van Leusen R. Results of protein and non-protein loading tests in patients with hepatocerebral intoxication. Digestion 1972; 6: 245.
8. Vernon PE. Theories of intelligence. In: Intelligence, heredity and environment. WH Freeman and Company, USA 1979: 39-53.
9. Kardel T, Lund Y, Zander Olsen P, Möllgaard V, Gammeltoft A. Encephalopathy and portocaval anastomosis. Scand J Gastroenterol 1970; 5: 681-5.
10. Quero JC, Groeneweg M, Meulstee J, Hop WCJ, Schalm SW. Does a low-dose of lactulose improve quality of life in patients with liver cirrhosis? In: Record CO (Ed). Advances in hepatic encephalopathy and metabolic nitrogen exchange. CRC Press 1996, Boca Raton, USA.
11. Tarter RE, Hegedus AM, Van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of evidence of overt hepatic encephalopathy. Gastroenterology 1984; 86: 1421-1427.
12. Quero JC, De Bruijn I, Hartmann IJC, Schalm SW. Does subclinical hepatic encephalopathy affect quality of life? Gastroenterology 1995; 108: A1151.

Chapter 8

SUMMARY
SAMENVATTING

Subclinical hepatic encephalopathy (SHE) is a syndrome in which patients with liver cirrhosis without clinical signs of overt hepatic encephalopathy demonstrate a number of quantifiable neuropsychological and/or neurophysiological defects. Chapter 1 gives a review of the literature concerning the diagnostic methods used for detection of SHE, its clinical significance, and the intervention studies performed. The prevalence of SHE has been reported to vary between 30% to 80%. This large variation in prevalence is caused by a lack of a 'gold standard' diagnostic test, differences in the definition of SHE, the diagnostic methods used, the definition of normal values, and the patient population tested. Early studies suggested that SHE had clinical significance as, theoretically, it would develop in overt clinical encephalopathy, and have a negative impact on patients' daily life (e.g., in driving a car, or working with machinery). However, recent studies have failed to show the negative influence of SHE on fitness to drive. In addition, intervention studies have not made use of parameters of daily functioning to monitor the effect of treatment efficacy in SHE. Studies in which the clinical relevance of this subclinical entity is evaluated should be performed before screening for SHE or treatment is recommended.

Although the arterial ammonia concentration correlates best with the severity of hepatic encephalopathy, arterial punctures for investigational purposes can cause medical ethical problems in some countries. In Chapter 2 we compared capillary ammonia levels with arterial ammonia levels simultaneously determined with the Blood Ammonia Checker II. Agreement was poor as capillary ammonia levels were considerably higher than arterial ammonia levels. Furthermore, capillary ammonia measurements showed poor

reproducibility. Capillary ammonia measurements are, therefore, unreliable for monitoring patients with hyperammonaemic diseases.

In Chapter 3, two psychometric tests (NCT, SDT) and automated EEG analysis were used for the diagnosis of SHE in 137 patients with liver cirrhosis. Results show that without the use of age-dependent normal values, the prevalence of SHE is largely overestimated. There is poor overlap between abnormal psychometric tests and neurophysiological tests, suggesting that both methods probably measure different components of SHE. The prevalence of SHE is low (14%) in patients with Child-Pugh grade A, and increases to 45% in Child-Pugh grade B or C. The most remarkable finding of this study is that older patients with an elevated arterial ammonia concentration are more prone to develop SHE than younger patients with an equal arterial ammonia concentration.

The influence of chronic liver disease on patients daily functioning was assessed using the Sickness Impact Profile (SIP) questionnaire in 100 cirrhotic patients (Chapter 4). The distribution of the SIP scores of the patients with liver cirrhosis differed from the reference scores of the normal population. Patients with SHE had a worse SIP score than those without SHE. Multivariate analysis showed that the impaired daily functioning was not related to age or severity of liver disease. The reproducibility of the SIP results was high when the test was repeated after a 3-month period.

In Chapter 5 the effect of a low dose of lactulose (30 grams daily) on psychometric tests, spectral EEG, and daily functioning in hyperammonaemic cirrhotic patients was evaluated. Forty patients participated in a 6-months

double-blind placebo controlled study. No significant changes were seen after treatment in the arterial ammonia concentration, psychometric tests, spectral EEG and total SIP score in both the lactulose and placebo group. A low-dose of lactulose is, therefore, not effective in hyperammonaemic patients with respect to SHE and quality of life. Whether patients with SHE and impaired quality of life will benefit from effective treatment (higher lactulose dose?) remains to be determined.

Helicobacter pylori infection in patients with liver cirrhosis could be a risk factor for hepatic encephalopathy, as H pylori produces large amounts of ammonia in the stomach. A study was performed in 11 hyperammoneamic cirhotic patients infected with H pylori, in which the effect of H pylori eradication therapy on the arterial ammonia levels was assessed (Chapter 6). H pylori eradication resulted in a significant reduction of baseline blood ammonia levels from 79 μmol/l to 64 μmol/l. Ten weeks after treatment the mean blood ammonia level had risen to 79 μmol/l, which was not significantly different from baseline values. It is concluded that H pylori eradication does not result in a long-term reduction in blood ammonia levels in hyperammonaemic patients. Reduction of ammonia after treatment can be explained by the non-specific effect of amoxycillin on ammonia-producing gut flora, rather than the eradication of the ammonia-producing H pylori itself.

In Chapter 7 a discussion on the mysterious entity SHE is given. It is questionned whether expensive and time consuming tests should be performed in patients who do not have any complaints. A proposal is made to screen patients with SHE for impaired daily functioning. Future research should be directed to the development of simple diagnostic tools, which measure SHE and impaired daily functioning.

Subklinische hepatische encefalopathie (SHE) is een syndroom waarbij patiënten met levercirrose zonder klinische symptomen van hepatische encefalopathie, afwijkingen vertonen bij neuropsychologisch en/of neurofysiologisch onderzoek. Hoofdstuk 1 geeft een literatuur-overzicht van de diagnostische methoden die worden gebruikt voor de detectie, de klinische betekenis en behandeling van SHE. De prevalentie van SHE bij patiënten met levercirrose varieert in de literatuur van 30% tot 80%. Deze grote spreiding wordt veroorzaakt door het ontbreken van een 'gouden standaard' diagnostische test, verschillen in de definities van SHE, de gebruikte diagnostische methoden, de definitie van normaal en de onderzochte patiënt populatie. De eerste studies suggereren dat SHE van klinische betekenis is, omdat SHE in klinische encefalopathie zal overgaan en een nadelige invloed op het dagelijks leven van de patiënt zal hebben (bijvoorbeeld bij het besturen van een auto of bedienen van een machine). Recentere studies hebben echter geen nadelig effect van SHE op het besturen van een auto kunnen aantonen. Tevens is in de tot nu toe verrichte interventie-studies dagelijks functioneren nooit als parameter gebruikt ter beoordeling van de effectiviteit van behandeling van SHE. Voordat behandeling van SHE kan worden aanbevolen, moeten eerst studies worden verricht naar de betekenis van deze subklinische entiteit.

Hoewel de arteriële ammoniak concentratie het best correleert met de ernst van hepatische encefalopathie, kan het verrichten van arterie-puncties voor onderzoeksdoeleinden in veel landen op medisch-ethische bezwaren stuiten. In Hoofdstuk 2 werden capillaire met arteriële ammoniak spiegels vergeleken met behulp van de zogenaamde Blood Ammonia Checker II. Arteriële en capillaire ammoniak spiegels kwamen slecht overeen, waarbij de capillaire ammoniak

spiegels steeds hoger uitvielen. Tevens was de reproduceerbaarheid van de capillaire ammoniak metingen slecht. Capillaire ammoniak metingen zijn derhalve niet betrouwbaar voor het vervolgen van patiënten met hyperammonaemische ziekten.

In Hoofdstuk 3 werden twee psychometrische testen (NCT, SDT) en het spectraal EEG gebruikt om SHE te diagnosticeren in 137 patiënten met levercirrose. De resultaten toonden dat de prevalentie van SHE overschat wordt, wanneer geen gebruik wordt gemaakt van normaalwaarden gecorrigeerd voor leeftijd. Er was weinig overlap tussen abnormale psychometrische testen en abnormale spectraal EEG's, hetgeen suggereert dat beide methoden mogelijk een verschillend aspect van SHE meten. De prevalentie van SHE (14%) was laag in patiënten met Child-Pugh graad A leverziekte en steeg naar 45% in Child-Pugh graad B of C leverziekte. Een opmerkelijke bevinding van deze studie was dat oudere mensen met een verhoogde arteriële ammoniak spiegel een grotere kans hebben op SHE dan jongere patiënten met dezelfde arteriële ammoniak spiegel.

De invloed van chronische leverziekte op het dagelijks functioneren van patiënten werd beoordeeld met behulp van de Sickness Impact Profile (SIP) vragenlijst bij 100 patiënten met levercirrose (Hoofdstuk 4). De resultaten lieten zien dat de verdeling van de SIP scores anders is bij patiënten met levercirrose dan in de normale populatie. Patiënten met SHE hadden een slechtere SIP score dan patiënten zonder SHE. Multivariaat analyse toonde aan dat het verminderde dagelijkse functioneren niet het gevolg is van de leeftijd of van de ernst van de leverziekte. De reproduceerbaarheid van de SIP was goed bij het herhalen van

de vragenlijst na 3 maanden.

In Hoofdstuk 5 werd het effect van een lage dosis lactulose (30 gram d.d.) op psychometrische testen, spectraal EEG en dagelijks functioneren in hyperammonaemische cirrose patiënten geëvalueerd. Veertig patiënten namen deel aan een 6 maanden durende dubbelblinde, placebo-gecontroleerde studie. Na behandeling werden noch in de lactulose-, noch in de placebo-groep, significante veranderingen gezien in de arteriële ammoniak concentratie, psychometrische testen, het spectraal EEG en de SIP score. Een lage dosis lactulose is derhalve niet effectief in de behandeling van SHE en verbetering van kwaliteit van leven bij hyperammonemische patiënten. Of patiënten met SHE én een verminderd dagelijks functioneren baat zullen hebben bij een meer effectieve behandeling (hogere lactulose dosering?) dient nog onderzocht te worden.

Helicobacter pylori infectie in patiënten met levercirrose zou een risicofactor kunnen zijn voor het ontstaan van hepatische encefalopathie, omdat H pylori grote hoeveelheden ammoniak in de maag produceert. Een studie werd verricht in 11 hyperammonaemische cirrose-patiënten, die met H pylori geïnfecteerd waren, waarbij het effect van H pylori eradicatie-therapie op de arteriële ammoniak-spiegels werd bestudeerd (Hoofdstuk 6). H pylori eradicatie leidde tot een significante daling van de arteriële ammoniak spiegels van 79 μmol/l naar 64 μmol/l. Tien weken na behandeling was de gemiddelde arteriële ammoniak spiegel echter weer gestegen naar 79 μmol/l, wat niet significant verschillend was van de uitgangswaarde. Er wordt geconcludeerd dat H pylori eradicatie niet leidt tot een blijvende verlaging van de ammoniak-spiegels in het

bloed van hyperammonaemische patiënten. De verlaging van de ammoniak-spiegel na behandeling kan verklaard worden door het aspecifieke effect van amoxicilline op de ammoniak-producerende darmflora in plaats van door de eradicatie van H pylori.

Hoofdstuk 7 is een discussie over de mysterieuze entiteit SHE. Men dient zich af te vragen of het zinvol is om kostbare en tijdrovende diagnostiek te verrichten bij patiënten die geen klachten hebben. Een voorstel wordt gedaan om in toekomstig onderzoek naar SHE meer aandacht te besteden aan de diagnostiek van verminderd dagelijks functioneren.

DANKWOORD

Veel mensen hebben, direct of indirect, bijgedragen aan de totstandkoming van dit proefschrift.

Mijn promotor Solko Schalm wil ik bedanken voor het vertrouwen dat hij mij gaf in het opzetten van mijn eigen onderzoekslijn, welke volledig afweek van wat hij oorspronkelijk voor ogen had op het moment dat hij mij in dienst nam. Zijn kritische opmerkingen waren niet alleen leerzaam, maar ook een uitdaging tot perfectionering.

De afdeling Klinische Neurofysiologie heeft aanzienlijk bijgedragen aan mijn onderzoek. Zonder tekort te doen aan het gehele personeel van deze afdeling, wil ik in het bijzonder Jan Meulstee, Marijke de Waart en Ton Mus bedanken, die steeds tijd voor mij vrij maakten om me met mijn onderzoek te helpen.

Wim Hop is voor mij van onschatbare waarde geweest. Niet alleen vanwege zijn hulp bij de statistische analyse van het onderzoek, maar ook bij het de mond snoeren van reviewers, die op onjuiste statistische gronden publicaties probeerden tegen te houden.

De voortgang van het onderzoek was mede mogelijk door hulp van enthousiaste studenten. Ieneke Hartmann, Ilone de Bruijn, Sylvia Beyeman en Ismail Sevinc zijn ongetwijfeld gek geworden van de, voor mij overzichtelijke, chaos.

Alle co-auteurs wil ik bedanken voor hun bijdrage aan de totstandkoming van de artikelen.

Iedereen van het secretariaat Hepatologie was zeer behulpzaam bij de opzet, voortgang, verwerking en afronding van het onderzoek.

Ook de poli-assistentes van de polikliniek Interne Geneeskunde II, die gek

werden van de ongebruikelijke aanvragen, mag ik zeker niet vergeten.
Mijn 'klapper' in de Lancet was niet mogelijk geweest zonder de hulp en expertise van het personeel van lab. Interne Geneeskunde II.
Met mijn opvolger, Michael Groeneweg, had ik (tijdens het squashen) levendige wetenschappelijke discussies, die mij stimuleerden om het proefschrift te voltooien. Door hem steeds lastig te vallen met allerlei dingen, die hij voor mij moest regelen terwijl ik in Dordrecht zat, heb ik kunnen voorkomen dat hij eerder zou promoveren dan ik.
Mijn paranimfen, René van der Hul en Peter Plaisier, wil ik bedanken voor de waardevolle hulp bij de afronding van het proefschrift en hun pure vriendschap.

Solvay Pharma B.V. wil ik bedanken voor de hulp tijdens mijn onderzoek en de financiële bijdrage aan het proefschrift. Het drukken van dit proefschrift werd tevens mede mogelijk gemaakt met de financiële bijdrage van de firma's Astra Pharmaceutica B.V., Glaxo Wellcome B.V., Schering-Plough B.V., Tramedico B.V. en Zambon B.V..

Tot slot, wil ik uiteraard Rosa bedanken voor haar geduld tijdens de saaie avonden en weekenden, die ik gebruikte om aan dit proefschrift te werken.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren of 28 april 1966 te Melilla (Spanje). Hij volgde het V.W.O. aan de scholengemeenschap Spieringshoek te Schiedam, alwaar hij in mei 1984 zijn diploma behaalde (Atheneum-B). In september 1984 werd begonnen met de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Van september 1988 tot juli 1989 was hij werkzaam op het laboratorium Inwendige Geneeskunde III van het Academisch Ziekenhuis Rotterdam als student-assistent, alwaar onder supervisie van Prof. Dr G. Hennemann en Prof. Dr T.J. Visser onderzoek werd verricht naar transport en metabolisme van schildklierhormoon. Hij behaalde het artsexamen op 19 april 1991. Van mei 1991 tot juni 1995 was hij werkzaam op de afdeling Inwendige Geneeskunde II van de Erasmus Universiteit Rotterdam (hoofd Prof. J.H.P. Wilson). Tijdens deze periode werd onder begeleiding van Prof. Dr S.W. Schalm klinisch onderzoek verricht op het gebied van hepatische encefalopathie, hetgeen de basis vormde voor dit proefschrift. Sinds juli 1995 volgt hij de opleiding tot internist in het Merwedeziekenhuis te Dordrecht (opleider Dr J. van der Meulen).