Diagnosis of Minimal Hepatic Encephalopathy

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Minimal hepatic encephalopathy (mHE) has significant impact upon a liver patient's daily living and health related quality of life. Therefore a majority of clinicians agree that mHE should be diagnosed and treated. The optimal means for diagnosing mHE, however, is controversial. This paper describes the currently most frequently used methods—EEG, critical flicker frequency, Continuous Reaction time Test, Inhibitory Control Test, computerized test batteries such as the Cognitive Drug Research test battery, the psychometric hepatic encephalopathy score (PHES) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)—and their pros and cons. (J CLIN EXP HEPATOL 2015;5:S54–S59)

The concept of minimal hepatic encephalopathy (mHE) has been developed in the 1970s when people working in the field of hepatic encephalopathy became aware of the fact that some patients with liver cirrhosis who appeared normal on clinical examination showed either alterations of their electroencephalogram (EEG) or achieved pathological results in simple neuropsychological tests. Thereafter a multitude of studies was performed to assess the clinical course of mHE, its impact upon quality of life, its prognostic value or its meaning for a patient's daily functioning with respect for example to the ability to drive a car or to work with possibly harmful machines. Even more studies dealt with the neuropsychological characteristics of mHE and assessed different diagnostic means to identify the optimal approach for diagnosing mHE. In spite of tremendous efforts to find a gold standard so far this topic is still controversial. The methods assessed for their use to diagnose mHE include visual and automated EEG analysis, exogenous and endogenous evoked potentials, single paper-pencil tests like the Number Connection Tests, batteries of paper-pencil tests (e.g. PSE-Syndrome-Test, Repeatable Battery for the Assessment of Neuropsychological Status—RBANS),

computer-based tests (like the Inhibitory Control Test—ICT, Continuous Reaction Time Test (CRT) or Stroop Test) or test batteries such as the Cognitive Drug Research test battery, and a psychophysiological measure, the critical flicker frequency (CFF). The various methods assessed tend to represent the spirit of the time when they were first evaluated; however some have outlasted several of their followers. A current example for the impact of trends on mHE diagnosing is the recent recommendation of the Stroop smartphone application for this purpose,¹ an example for longevity is the EEG.

REQUIREMENTS FOR A SUITABLE DIAGNOSTIC MEANS FOR MINIMAL HE

Any measure used for diagnosing minimal HE should meet the following requirements: validity, objectivity, reliability, sensitivity and specificity. In other words: 1) It should represent the neuropsychiatric abnormalities present in HE (validity); 2) the test procedure, test evaluation and interpretation must be standardized and thus independent from the tester (objectivity); 3) repeated measures in a subject with clinically stable status provide similar results (re-test reliability); 4) patients with manifest HE can be reliably separated from healthy controls due to a high sensitivity and specificity. In addition the measure should be not time-consuming, easily to apply and cheap.

CURRENTLY USED MEASURES OF MINIMAL HE

Electroencephalography (EEG)

The EEG is used for diagnosing hepatic encephalopathy since the 1950s, when Foley, Watson and Adams observed characteristic monomorphic 2 per second waves in the frontal regions in patients with clinically overt HE.² Thereafter other groups described a gradual slowing of the EEG

Keywords: minimal hepatic encephalopathy, diagnostic means, diagnostic use, sensitivity, specificity

Received: 22.12.2013; **Accepted:** 5.6.2014; **Available online:** 31.7.2014

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Abbreviations: CDR: cognitive drug research; CFF: critical flicker frequency; CRT: continuous reaction time test; ICT: inhibitory control test; EEG: electroencephalography; mHE: minimal hepatic encephalopathy; PHES: psychometric hepatic encephalopathy score; PSE: portosystemic encephalopathy; RBANS: repeatable battery for the assessment of neuropsychological status; TA: target accuracy; WL: weighted lures

<http://dx.doi.org/10.1016/j.jceh.2014.06.005>

activity with increasing grade of HE.^{3,4} Parsons-Smith and co-workers developed a grading system for the EEG assessment in patients with liver cirrhosis which was used worldwide for a long time.⁴ This system comprised 5 groups of alterations: normal EEG (grade 0), generalized suppression of alpha-rhythm and its replacement by beta activity (grade A), unstable alpha-rhythm with random bouts of 5–7/s waves particularly over the temporal lobes (grade B); alpha-rhythm disturbed by runs of 5–6/s activity with predominance over the temporal and frontal regions (grade C); overall 5–6/s activity (grade D); replacement of 5–6/s activity by 2/s rhythms which spread backwards from the frontal regions over the hemispheres (grade E). A comparison of these EEG alterations with clinical findings showed a fair correlation, however none of the EEG findings was diagnostic for a specific grade of HE. This was confirmed by Penin in a study including 256 patients.⁵ He pointed out that in general deterioration or amelioration of liver function in his patients was accompanied by a corresponding change of the EEG. However, he also demonstrated that a normal EEG may exist in a patient with clinically overt HE and a pathological one in a patient without clinical signs of HE. The latter would be interpreted as indication of minimal hepatic encephalopathy.

EEG analysis for diagnosing HE has been significantly refined over the years, and visual EEG analysis has been replaced by computerized analysis. Initially EEGs were graded according to the mean dominant frequency and the relative amount of theta and delta activity.⁶ Later on, besides the temporal also spatial information (Short Epoch Dominant Activity Clustering Algorithm—SE-DECA) was used for classification,⁷ and more recently an inter- and intrahemispheric coherence analysis of the different frequency bands was added to the basic analysis of the mean dominant frequency.⁸

The EEG is without doubt a valid, objective and reliable means for diagnosing brain dysfunction. A major advantage is the independency from age, education and cultural effects, which is in contrast to neuropsychological tests. However, the sensitivity of the EEG for low grades of HE is limited and thus its use for diagnosing minimal HE is controversial. Parsons-Smith and co-workers observed EEG alterations in 43% of their patients despite of a normal clinical status.⁴ Using spectral analysis Amodio and co-workers observed pathological slowing of the EEG in 31 of 100 cirrhotic patients without clinical signs of HE.⁹ In contrast we found EEG alterations with visual as well as computerized analysis in only 17% of patients without clinical signs of HE and in only 35% of the patients with grade I HE.¹⁰ Our findings were corroborated by Montagnese et al who observed alterations of the EEG considering mean dominant frequency and the percentage of theta and delta activity in only 8.5% of their cirrhotic patients without clinical signs of HE (7% in clinically and neuropsychologically unaffected patients, 15% in patients with

normal clinical status but pathologic findings in psychometric tests), and only 50% of the patients with clinically overt HE.⁷ With respect to these data the EEG cannot be recommended for diagnosing minimal EEG, while it could be useful for follow-up examinations and the estimation of a patient's prognosis. EEG alterations in patients with liver cirrhosis indicate an increased risk of overt HE and death.⁸

Critical Flicker Frequency (CFF)

The critical flicker frequency has been used in the past as psychophysiological means for assessing the effect of drugs upon central nervous system function. It was recommended for diagnosing minimal HE in 2002,¹¹ and has been evaluated since by several groups. For CFF assessment light pulses are presented to a subject in decreasing frequency (usually from 60 Hz downwards) and the subject has to press a button as soon as the impression of fused light switches to flickering light. After a training session flicker frequencies are measured 8 times and the mean value of these runs is calculated as CFF. It is important to consider that the CFF significantly depends on the experimental setting—the color and luminance of the stimuli, the distance between the light source and the subject's eye, the visual angle and others—and upon age. Thus, norm data have to be elaborated for the specific equipment used, and cannot be adopted. Moreover, the CFF assessment requires intact binocular vision and absence of red-green blindness.

CFF has been shown to be of prognostic value, both, with regard to the development of overt HE as well as with regard to mortality.^{12,13} Nevertheless the use of CFF analysis for diagnosing minimal HE is controversial. Again an independence from numeracy, literacy and education can be considered as an advantage. However, currently available studies have shown that CFF cannot be performed by a considerable amount of patients and that sensitivity and specificity of CFF are only moderate. While Kircheis et al describe a sensitivity and specificity by definition of about 100% in their study with regard to clinically overt HE, Goldbecker et al,¹⁴ for example, found a sensitivity of only 40% studying patients with grades I or II HE. The reason behind the differing results is probably the difference in defining normal values. Several groups have shown an age-dependency of CFF with a decrease of the CFF-values of 0.6–0.7 Hz/life decade.^{11,14,15} Thus a fixed cut-off is prone to generate falsely pathological results in the more elderly patients.

Of interest, there are only few data of CFF in patients with overt HE. The majority of studies deal with minimal HE, and compare CFF data to those achieved by psychometric tests. Thereby it became obvious that while there is a correlation between CFF and psychometric test results considering the whole study population, the results are not superimposable when patients are subdivided into groups

with normal or pathological results.^{11,12,14–16} Kircheis et al found pathological CFF in 30% of 50 cirrhotic patients without overt HE compared to 50% pathological results using computerized psychometry.¹¹ Dhiman et al achieved pathological CFF in 21 of 100 cirrhotic patients without overt HE while 48 patients had a pathological psychometric hepatic encephalopathy score (PHES). Both test results were pathological simultaneously in 17 patients.¹⁵ Goldbecker et al report a pathological PHES in 23 out of 99 patients on the waiting list for liver transplantation compared to 14 pathological CFF results.¹⁴ Twenty-two of the 99 patients had grade I or II overt HE. PHES was pathological in 4 without clinical signs of HE and CFF in five. Lauridsen et al compared CFF and Continuous reaction time test (CRT) in 154 cirrhotic patients without overt HE and had pathological CFF results in 32% compared to 48% in the CRT test, both measures were pathological in 20%.¹⁶

Kircheis et al as well as Goldbecker et al showed a significant impact of the etiology of liver disease upon CFF results.^{11,14} Patients with alcoholic liver disease achieved significantly lower CFF than those with cirrhosis of other causes. Today studies that explicitly analyze the impact of concomitant disorders such as renal dysfunction, diabetes mellitus, hepatitis C or autoimmune disorders on CFF are lacking, but are needed for further evaluation of the specificity of the method for diagnosing HE.

CFF seems to be not that easily to apply as it could be expected on the first view. Lauridsen et al pointed out that 11% of the patients considered for their study of CFF and CRT were unable to complete the CFF measurements due to problems focusing on the light diode or fogging of the glasses.¹⁶ A similar experience had Goldbecker et al, who found 8 out of 99 patients unable to perform the task.¹⁴

Considering the low sensitivity CFF should not be used as first line method for diagnosing HE, but instead—similar to the EEG—as a follow-up measure. Here the method benefits from showing no learning effects.^{11,14}

Continuous Reaction Time Test (CRT)

The CRT has so far been used for diagnosing minimal HE predominantly in Denmark. The CRT assesses the reaction time in response to one-hundred 500 Hz tones presented in random intervals of 2–6 s via headphones. Patients with overt HE show an increase of both, the reaction time and its intra-individual variability compared to controls. The variability of the reaction time decreases with improvement of a patient's condition and increases even before a patient shows clinical symptoms of HE.¹⁷ The CRT variability is represented by the so-called CRT-Index (CRT-Index: 50th RT percentile/(90th–10th percentile)).¹⁸ Considering the data of healthy controls and patients with organic brain disease of other causes than liver disease a CRT-Index of >1.9

was defined as normal. The CRT results depend on attention and motor speed. According to data from Elsass et al¹⁸ and Lauridsen et al¹⁹ the CRT results do not depend on age or sex and do not show any learning effects. Further studies must clarify if and to which amount the CRT results are affected by concomitant disorders of HE such as hyponatremia, diabetes mellitus, renal dysfunction, alcoholism or hepatitis C, for example. In addition, the sensitivity and specificity of the test need to be further evaluated.

Inhibitory Control Test (ICT)

The Inhibitory Control Test is a test of higher executive functions assessing attention and response inhibition. Like the CRT the ICT is computer-based. Subjects are requested to press a button if in a random series of letters shown on a computer screen an X is followed by a Y. Within the letter series about 40 times pairs of XX or YY—the so-called lures—appear besides the target pair XY. The subjects tend to hit the button also for the lures but must inhibit this response. The test takes about 14 min.²⁰

Patients with minimal HE as diagnosed by psychometric tests or EEG show a significantly higher response rate to lures than controls or patients without mHE.^{20–22} Therefore initially the number of lures was recommended as measure of mHE. Bajaj et al suggested a cut-off between normal and pathological lure rates of 5 lures.^{20,21} By considering only the number of lures, however, cognitive dysfunction remains undetected in those subjects who respond to none or only a few stimuli at all. Therefore, Amodio et al recommended taking into account also the number of correct responses to targets. They observed that patients with liver cirrhosis had a response rate to targets of 40%–100% compared to 90%–100% in healthy controls.²² They also observed a U-shaped relationship between target accuracy and lures in patients with cirrhosis. Lures did neither correlate with the psychometric hepatic encephalopathy score (PHES) nor with the mean dominant frequency of the EEG or the CFF. The adjustment of the Lures result by the target accuracy was better in discriminating patients with mHE according to the other tests applied (PHES, EEG and CFF) from those without mHE. However, this ratio between Lures (L) and target accuracy (TA) called weighted lures ($WL = L/(TA)^2$) was outweighed by the target accuracy as stand alone variable. Of interest, Amodio et al observed an impact of education but not age on the number of lures in controls, and a learning effect in the patients.²² Goldbecker et al confirmed the effect of education but observed also an age effect upon both, the number of lures and weighted lures in the ICT.¹⁴ Re-examinations after 6–8 months showed a learning effect for lures, weighted lures and target accuracy in healthy controls. Applying norms adjusted for age and education Goldbecker et al achieved pathological ICT results in only 19% of patients with clinical overt HE for lures, in 43%

for weighted lures and in 86% for target accuracy.¹⁴ Thus, finally target accuracy seems more appropriate than the number of lures for diagnosing hepatic encephalopathy. As for the CRT further studies are needed to clarify the influence of concomitant disorders upon ICT results as well as sensitivity and specificity in detail.

Computerized Test Batteries

Computerized test batteries are used for diagnosing cognitive dysfunction with increasing frequency. There is only limited knowledge, however, with regard to their use in diagnosing minimal HE. Mardini et al compared the results of the Cognitive Drug Research test battery with the PHES in 89 cirrhotic patients without clinical signs of HE and found a significant correlation between test results.²³ Considering the PHES result as indicator of mHE the CDR had a sensitivity of 86.4% for mHE and a specificity of 81%. Data from patients with overt HE were not provided. Kircheis et al used 5 computerized tests from the Vienna Test System (Dr. Schuhfried Inc., Mödling, Austria) for diagnosing mHE.¹¹ Test results were considered abnormal if they were outside 1 standard deviation (SD) from the mean, a diagnosis of mHE was made if in 2 or more of the computerized psychometric tests at least one of the achieved test parameters were abnormal. Overall the 5 tests yielded 22 test parameters. Applying this definition “abnormal” test results were achieved in all patients with overt HE, 50% of the patients without clinical signs of HE and 10% of healthy controls. The battery had an optimal sensitivity, but an insufficient specificity for the purpose of diagnosing mHE with accuracy although the tests chosen (i. a. a computerized visual pursuit test, the Cognitrone test, the motor performance series, and the Vienna reaction time Measurement) are suitable for the detection of cognitive dysfunction characteristic for HE, on principle. The criteria for abnormality of the test results facilitated false positive results. Usually psychometric test results are considered abnormal if they exceed 2 standard deviations (SD) from the mean.

Psychometric Hepatic Encephalopathy Score (PHES)

The Psychometric Hepatic Encephalopathy Score (PHES) is the sum score achieved from the five sub-tests of the PSE (Portosystemic Encephalopathy)-Syndrome-Test, a paper-pencil test battery.²⁴ The PSE-Syndrome-Test comprises the Number Connection Tests A and B, a Digit Symbol Test, the Serial Dotting Test and the Line Tracing Test. The test has been developed and standardized in Germany. Meanwhile, however, norms have been prepared also for example for the Italian,⁹ Spanish,²⁵ Polish,²⁶ South Korean²⁷ and Mexican population,²⁸ and the test has been used also in India after replacement of the Number Connection Test B by a Figure Connection Test.²⁹ The

test assesses attention, visuo-spatial perception, visuo-spatial construction, psychomotor speed and motor accuracy, and thus those domains that have been shown to be affected by hepatic encephalopathy.^{30,31}

The cut-off value between normal and abnormal results of −4 points has been derived from the test results in patients with overt HE, healthy controls and a patient control group comprising subjects with inflammatory bowel disease.³¹ Using this cut-off the sensitivity of the test was 96% and the specificity 100%. Accordingly it was recommended to make the diagnosis of minimal HE if a patient with liver cirrhosis but no clinical signs of HE achieves a PHES of less than −4 points. This was the case in about 25% (14 of 63) of the cirrhotic patients without overt HE in the standardization study, but varies between different populations studied so far ranging from about 20 to about 50%. The test is available in four parallel versions, and thus can well be used for follow-up examinations. The test-retest reliability has been shown to exceed 0.81.²⁴ Using the four parallel test versions Ennen was able to show the absence of significant learning effects upon the PHES when the test was applied every two weeks.³² Of note, some of the sub-tests showed significant learning effects. These, however, were balanced in the composite score of the whole battery. Recently Goldbecker et al confirmed the absence of learning effects for the PHES repeating the test battery in healthy controls about 6 months after the first application.¹⁴

The PHES has been proven to be of diagnostic as well as prognostic use.^{15,31,33,34} A pathological PHES was shown to be predictive for both, the occurrence of an episode of overt HE^{33,34} and survival^{15,34} and to be able to identify cirrhotic patients who are at risk of falls within 1 year after the testing.³⁵ The PHES as well as the results of the sub-tests show a significant correlation to the cerebral glucose utilization in patients with liver cirrhosis and grades 0–II HE indicating the ability of the PHES to represent cerebral dysfunction in these patients.³⁶ The cortical glucose utilization decreases with decreasing PHES with predominance in inferior frontal and dorsolateral frontal regions.³⁶

Currently the test is often used as “gold standard” for diagnosing minimal HE (see for example Refs. ^{12,37–41}). The PHES has been recommended for diagnosing minimal HE by expert groups repeatedly.^{42,43} The test was distributed by SWETS Test Services initially, and until recently by Pearson.²⁴ Currently Hannover Medical School holds the copyright for the test and provides the test material via the author of this article.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS has been recommended for diagnosing HE by a working group formed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) to review available data for the neuropsychological

assessment of hepatic encephalopathy.⁴³ The working group recommended the RBANS predominantly for use in the USA as there population-based standardization and norming had been performed for the RBANS, but not for the PSE-Syndrome-Test, which was recommended as well. The RBANS addresses verbal and visual anterograde memory, working memory, cognitive processing speed, language and visuo-spatial function, and thus cognitive functions which are not affected by HE besides those that are characteristically affected.^{30,31} The test battery has been developed for the assessment of dementia and screening of cognitive impairment in other disorders. So far, it has only rarely been used for diagnosing mHE,^{14,44–46} and data about sensitivity and specificity of the RBANS for diagnosing HE are scarce. We found a sensitivity of only 38% for diagnosing overt HE, and thus would not recommend the use of RBANS for diagnosing mHE.¹⁴

CONCLUSION

The optimal measure for diagnosing minimal HE is still controversial and the chances are that it will stay controversial. None of the methods used is able to cover all facets of HE as with use of appropriate norms none achieves a sensitivity of 100% for overt HE, while the rate of pathological results in patient groups without overt HE differs markedly and the results of the various methods are not consistent.^{14,16,34,47} This must be held in mind by everybody who uses one or the other method for diagnosing HE. A precondition for any measure used is the availability of reliable norms besides the requirements for validity, test–re-test reliability, sensitivity and specificity. This precondition is not met by all methods used, and is likely to be ignored if a method appears fashionable and easily to apply.^{1,48} Thereby, however, the concept of minimal hepatic encephalopathy will be damaged in the long term, and minimal HE—which has significant negative impact upon any patients daily life⁴⁹—is likely to be ignored by the majority of clinicians if standards of neuropsychological testing are violated in diagnosing mHE.

CONFLICTS OF INTEREST

The author took part in the standardization of the PSE-Syndrome-Test and the PHES and is authorized to distribute the test on behalf of Hannover Medical School.

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