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 (retest 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

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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
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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—SEDECA) 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