

Critical flicker frequency and continuous reaction times for the diagnosis of minimal hepatic encephalopathy. A comparative study of 154 patients with liver disease

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Abstract Minimal hepatic encephalopathy (MHE) is intermittently present in up to 2/3 of patients with chronic liver disease. It impairs their daily living and can be treated. However, there is no consensus on diagnostic criteria except that psychometric methods are required. We compared two easy-to-perform reproducible bedside methods: the critical flicker frequency (CFF) and continuous reaction times (CRT) tests. A CFF <39 Hz and CRT-index <1.9 (index: the ratio 50/(90 minus 10) percentiles of reaction times) indicates cerebral dysfunction. 154 patients with acute or chronic liver disease with out overt hepatic encephalopathy (HE) underwent both tests at the same occasion. Both tests were abnormal in 20% of the patients and both tests were normal in 40% of the patients. In more than 1/3 the two tests were not in agreement as CFF classified 32% and CRT-index classified 48% of the patients as having MHE ($p < 0.005$). The two tests were weakly linearly correlated ($r^2 = 0.14$, $p < 0.001$) and neither test correlated with the metabolic liver function measured by the Galactose Elimination Capacity (GEC), nor with the blood ammonia concentration. Both tests identified a large

fraction of the patients as having MHE and cleared only 40%. The two tests did not show concordant results, likely because they describe different aspects of MHE: the CFF gives a measure of astrocytic metabolic state and hence pathogenic aspects of MHE, whereas the CRT measures a composite key performance, viz. the ability of reacting appropriately to a sensory stimulus. The choice of test depends on the information needed in the clinical and scientific care and study of the patients.

Keywords Minimal hepatic encephalopathy · Subclinical hepatic encephalopathy · Critical flicker frequency · Continuous reaction time

Introduction

Minimal hepatic encephalopathy (MHE) is the designation for the cerebral dysfunction occurring in patients with liver disease without overt encephalopathy and where other causes of encephalopathy are excluded.

Up to two thirds of patients with cirrhosis may intermittently suffer from MHE (Prasad et al. 2007). MHE profoundly disturbs the patients' quality of life by compromising cognitive functions, social interactions, emotional behaviour, mobility and sleep (Groeneweg et al. 1998). Discrete deficits in attention, vigilance and orientation are often present along with slowing of psychomotor speed (Amodio et al. 2004; Bajaj 2008). MHE can render keeping meaningful family relations, a normal job or driving a car impossible (Ortiz et al. 2005; Schomerus and Hamster 2001). In most cases, it is possible to treat or improve the condition by means of nutrition therapy supplemented with lactulose or other pre- and probiotics or antibiotics (Prasad et al. 2007; Romero-Gomez 2010; Shukla et al. 2011)

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Because MHE is frequent, debilitating and treatable, it is important to be able to diagnose it and to follow-up on treatment effects. Yet, there is no golden standard and no professional consensus on how this is done (Dhiman et al. 2010; Ferenci et al. 2002; Randolph et al. 2009). The clinical criteria are based on presence of relevant liver disease, usually cirrhosis and/or porto-systemic shunts, and absence of overt hepatic encephalopathy (HE), e.g. slow-cerebration, confusion or stupor. The positive diagnosis of MHE requires an abnormal neuro-psychological test—and several such tests have been developed (Ortiz et al. 2005). For routine use, such tests have to be easily performed by clinical staff. In our department we have used the Continuous Reaction Times (CRT) test for many years. Other institutions prefer the Critical Flicker Frequency (CFF) test.

This study describes the single-center parallel clinical use of these two conceptually different computerized tests. We expected both tests to diagnose a considerable fraction of the patients as having MHE and we also expected both tests to identify the same patients as having MHE. The aim was to perform both tests on the same occasion in an unselected group of liver patients without overt HE. The test results were related to the patients' metabolic liver function and to their blood ammonia concentration.

Patients and methods

Patients The study population comprised 154 patients with liver disease who underwent a CFF and CRT test on the same occasion between September 2007 and November 2010. On the same day the metabolic liver function was assessed by the galactose elimination capacity test (GEC) in 98 patients and the serum ammonia concentration measured in 36. The patients were referred to the tests by the clinical hepatologists with the purpose of identifying MHE and decide on treatment. Most patients suffered from alcoholic liver disease (Table 1). The average patient age was 55 years (range 19–87, SD 11), and 36 of them were females and 118 males. Patients with signs of overt hepatic encephalopathy were not referred. Likewise, patients with other possible causes for cerebral involvement than the liver disease, eg. severe electrolyte disturbances, use of psychoactive drugs and alcohol withdrawal, were not referred. All the tests were conducted within the department by one of two laboratory technicians between 9:00 and 14:00 in an undisturbed location.

Critical flicker frequency In a pair of spectacles shielding against outside light the person watches a red diode light that pulses at a 1:1 ratio at a frequency of 60 Hz. At this high frequency the red light is perceived as fused. The light

Table 1 Diagnoses of 154 liver patients referred to CFF and CRT measurements at the same occasion

Diagnosis	Number of patients
Alcoholic cirrhosis	68
Acute liver failure on alcoholic basis	21
Hepatocellular carcinoma	16
Chronic hepatitis C	15
Idiopathic cirrhosis	11
Primary biliary cirrhosis	4
Portal vein thrombosis	4
Budd-Chiari syndrome	2
Primary sclerosing cholangitis	2
Vascular malformations	2
Non-alcoholic steatohepatitis	2
Liver transplantation follow-up	1
Ascites of unknown hepatic aetiology	1
Alcoholic fatty liver disease	1
Autoimmune hepatitis	1
Liver metastasis	1
Malformation of bile ducts	1
Malignant neoplasm of the bile ducts	1
Total	154

pulse frequency is then gradually decreased until the light is perceived as flickering or pulsating. The patient is instructed to press a handgrip button when this happens. Nine measurements are conducted and the patient's critical flicker frequency (CFF) is the average of the measurements. Each test, including patient instruction and data collection, takes 15 to 20 min. Based on a large normal and patient material, a CFF lower than 39 Hz is taken to indicate cerebral dysfunction (Kircheis et al. 2002). CFF was measured using a HEPAtonorm analyzer (Accelab GmbH, D-72127 Kusterdingen, Germany). Nineteen patients were unable to complete the measurements due to problems focusing on the light diode or fogging of the glasses. These patients were not included in the study population.

Continuous reaction time With the dominant hand the person holds a grip with a trigger button on top, connected via the signal generator to a laptop PC. The generator delivers 100 auditory signals at 500 Hz and 90 dB at random intervals of 2 to 6 s via a set of calibrated sound isolated headphones. The person is instructed to press the button with his thumb as soon as the signal is heard and the reaction time is registered. Reaction times above 2 s or no reaction before the next signal are registered as "no-response". The reaction times' 10th, 50th and 90th percentiles and their variation, the 'index' are calculated (index: the ratio 50/(90 minus 10) percentiles of reaction

times). Based on a large normal and patient material the index results in the best discrimination between patients with hepatic encephalopathy and other test populations, and a CRT-index <1.9 is abnormal (Elsass et al. 1981). Each test, including patient instruction and data collection takes 10 to 15 min. No patient was unable to complete the test. The equipment was an EKHO system (Bitmatic, Aarhus, Denmark) coupled to an ordinary laptop PC.

The galactose elimination capacity Following intravenous injection of galactose, repeated arterialized capillary blood samples were secured for 1 h and urine was collected quantitatively. Samples were analyzed for galactose concentration. The galactose elimination capacity (GEC) was calculated from the slope of the linear blood galactose concentration over time decay curve, corrected for urinary loss (Tygstrup 1964).

Blood tests Venous blood was secured in cooled, gas tight syringes for dry film enzymatic measurement of ammonia concentration. These analyses were performed according to standard certified clinical chemistry laboratory methods.

Statistical analysis Histograms showed that the results of the CFF, CRT, GEC and ammonia measurements could be described by the normal distribution. Correlations between test results were calculated using the Person r^2 . McNemar's test was used to evaluate the level of concordance between the CFF and CRT test results. p values below 0.05 were considered statistically significant.

Results

Table 2 shows the distribution of 154 patients who underwent both tests. Both test results were abnormal in 20% (31) of the patients and both tests were normal in 40% (61). Only 62% of the patients with an abnormal CFF had an abnormal CRT, and only 42% of the patients with an abnormal CRT had an abnormal CFF.

32% (50 patients) had a CFF-mean <39 Hz, indicating MHE and 48% (74 patients) had a CRT-index <1.9 ,

indicating MHE (Table 2). Hence, the two tests disagreed on the diagnosis in 40% of cases ($p<0.005$) (Table 2).

The two tests were weakly but significantly correlated (Fig. 1, $r^2=0.14$, $p<0.001$). The same was the case with the subgroup of patients with verified cirrhosis ($r^2=0.12$, $p=0.001$).

There was no correlation between the galactose elimination capacity and either psychometric test (Fig. 2). This was also the case in patients with cirrhosis.

There was no correlation between the patients' serum ammonia concentration and their CFF-mean or CRT-index.

Discussion

In accordance with our *a priori* expectations, both tests indicated MHE in one third to one half of the patients. However, the results of the tests were unexpectedly dissimilar. In almost half of the patients the two tests were discordant and categorized the patients differently.

Both tests were performed by skilled staff and according to the test guidelines. Our every-day use of the tests during the study confirmed that they were both easy to apply and acceptable to the patients although the CFF test resulted in more than 10% dropouts from the study. The test equipments were of the newest generation to enter clinical use. Published independent patient populations defined the cut-off values. The patients were referred to the tests by physicians well trained in recognizing overt encephalopathy and no such patient was referred.

It may seem surprising that such a high fraction of liver patients without overt HE did in fact have signs of MHE. Still, this finding is in accordance with several previous reports (Dhiman et al. 2010; Ferenci et al. 2002; Li et al. 2004; Prasad et al. 2007; Sharma and Sharma 2010). It emphasizes the need for routine psychometric screening of all liver patients. The clinical benefit of doing so is very large because MHE ruins the quality of the patients' life (Amodio et al. 2004; Bajaj 2008; Bao et al. 2007; Groeneweg et al. 1998; Kircheis et al. 2009a, b; Schomerus and Hamster 2001) and because the problem in the large majority of cases is treatable.

It would be highly desirable to reach a consensus and a standard for how to perform such screening. This would

Table 2 Distribution of test results. The McNemar's test with $p<0.005$ states that the test results were significantly discordant

		CFF-mean		
		Abnormal test result	Normal test result	Total CRT
CRT-index	Abnormal test result	20% ($n=31$)	28% ($n=43$)	48% ($n=74$)
	Normal test result	12% ($n=19$)	40% ($n=61$)	52% ($n=80$)
Total CFF		32% ($n=50$)	68% ($n=104$)	100% ($n=154$)

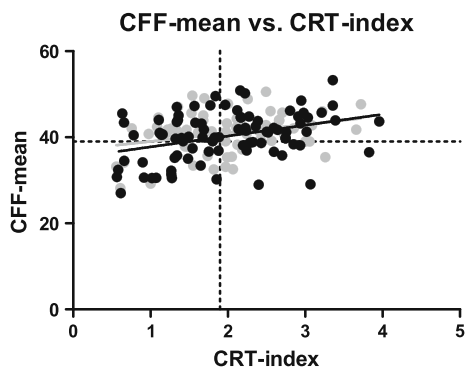


Fig. 1 Relation between the Continuous Reaction Time index (CRT-index) and the Critical Flicker Frequency mean (CFF-mean) measured in 154 clinically non-encephalopathic patients with liver disease. The dotted lines indicate cut-off values (CRT-index <1.9 and CFF-mean <39 Hz). The black dots represent patients with cirrhosis of the liver ($n=85$). The figure shows a weak but statically significant positive correlation between the two measures ($r^2=0.12$, $p=0.001$)

render uniform recommendations possible and secure treatment of most patients. Furthermore, it would be possible to conduct multi-centre trials and improve the treatment of MHE on the evidence-based level. A considerable number of complex or simple methods have been suggested and presented in selected patient populations (Amodio et al. 1996; Bajaj 2008; Groeneweg et al. 2000; Kircheis et al. 2009a, b; Montagnese et al. 2004). Unfortunately, however, it has not been possible to establish a standard. This study, which compares the performances of two of the simplest machine-based tests, illustrates the difficulties.

The lack of agreement between the tests was probably *not* due to characteristics of the study population. Restricting the study to patients with diagnosed cirrhosis or with alcoholic vs. non-alcoholic aetiology did not improve the agreement (Fig. 1). Use of opioids and tranquilizers might disturb the CRT more than the CFF—but patients on such medication were not included (Roback et al. 1952; Sjogren et al. 2000a, b; Sjogren 2000a, b; Smith and Misiak 1976). Selection bias, i.e. due to referral pattern, should not disturb the lack of agreement between the tests. Finally, we did not identify cut-off values that improved the agreement over that obtained by

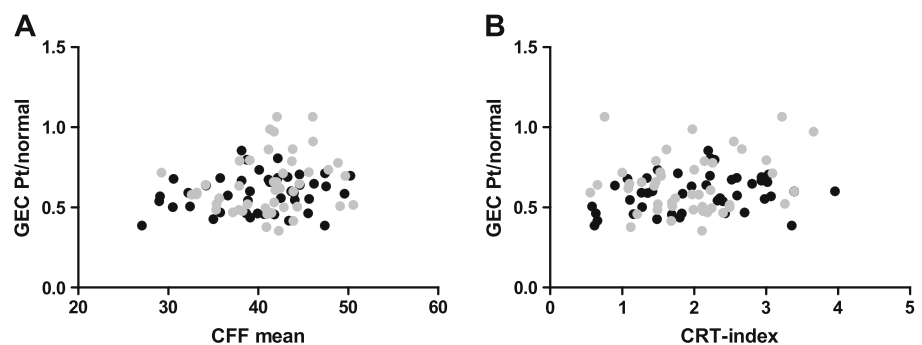
the use of the original cut-offs. Likewise, replacing the CRT-index with either the patients' slowest reaction times (the 90th percentile) or the fastest reaction times (the 10th percentile) did not improve the concordance with the CFF test results. The lack of concordance, therefore, should be ascribed to characteristics of the condition MHE, and to physiological characteristics of the tests.

MHE is a complex global neuropsychiatric brain function disturbance. There is no single manifestation that consistently pervades the clinical picture. One test therefore, cannot encompass the spectrum of deficits of the condition and hence cannot approve or dismiss all cases. Because there is no diagnostic gold standard for MHE a 'true' specificity and sensitivity of a test (or a battery) cannot be calculated. The diagnostic possibility is comparisons of tests, as in this study, and for interventional studies to choose those tests that measure the defined qualities of MHE that are under study.

The two tests we used here measure biologically and conceptually different aspects of MHE: the CFF test reflects biological activity in retinal cells, whereas the CRT test measures a personal performance. The CFF gives a measure of mitochondrial energy restoration capacity in the light sensitive retinal cells that are anatomically specialized astrocytes. The test, therefore, is taken to reflect astrocytic metabolic functional state (Haussinger et al. 2002) which plays a central role in prevailing hypotheses on the patho-aetiology of HE. The test gives information on visual processing, but also cognitive functions such as arousal and attention. In contrast, the CRT is a global senso-cognitive-motoric function measure of patient's ability to deliver a motor reaction adequately and repeatedly (Jakobsen et al. 2010). The test evaluates sustained attention, cerebral processing time, including reaction time and response inhibition, and nerve conduction speed. These differences are likely responsible for the disagreement between the tests.

There was no relationship between the residual metabolic liver function as measured by the GEC and either psychometric test. This was also unexpected because the GEC predicts the emergence of overt hepatic encephalopathy and the prognosis of cirrhosis patients (Jepsen et al. 2010). This

Fig. 2 Panel a CFF vs. GEC.
Panel b CRT vs. GEC



may indicate that subclinical compromised brain function and decreased liver function are dissociated manifestations of liver disease, and MHE and overt HE are differently related to the metabolic capacity of the sick liver.

In conclusion, the CFF- and the CRT- test both identified a large fraction of clinically non-encephalopathic liver patients as having MHE. The tests, however, did not show concordant results, likely because they describe different aspects of MHE. The choice of the CFF or the CRT test depends on the information needed in different settings of care and study of the patients.

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