Diagnosis of Minimal HE—And the Temptation of Easy Solutions

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The theoretical construct of minimal hepatic encephalopathy (mHE) has been developed in the 1970s when Zeegen and co-workers observed that part of the patients with liver cirrhosis who appeared normal in a clinical examination nevertheless showed significant cognitive alteration in psychometric tests.¹ Thereafter several groups made valuable contributions to the characterization of cognitive dysfunction in patients with “subclinical” HE, as mHE was called back then.^{2–4} By applying comprehensive psychometric test batteries they were able to show that mHE is characterized by deficits in attention, visual perception, visuo-spatial construction, motor speed and accuracy, especially, while other domains such as language or memory are spared. Despite of these excellent analyses which clearly pointed out that mHE cannot be described one-dimensional, there was a keen desire to find one simple measure that was able to diagnose mHE without demanding too much time and effort. A lot of different methods have been used since: the Number Connection Tests A and B, the Block Design Test and as the first neurophysiological means visually analyzed electroencephalograms (EEG) in the 1970s and early 80s, then computerized psychometric tests and evoked potentials as well as spectral EEG analysis in the 90s, critical flicker frequency in the beginning of the new century and finally the Inhibitory Control Test (ICT), a computerized test of attention and response inhibition in 2007.^{5–12}

In the present volume of the *Journal of Clinical and Experimental Hepatology* Taneja and co-workers present a study that compares the ICT with the sum score of the PSE-Syndrome Test PHES (psychometric hepatic encephalopathy score) for their use in diagnosing mHE.¹³ The PSE-Syndrome-Test—a paper-pencil-test comprising 5 subtests—is kind of a relict of the 1980s. It has been developed by the neuropsychologist Wolfgang Hamster and the hepatologist Hans Schomerus considering the results of a battery of more than 30 psychometric tests, EEG and critical flicker frequency in patients with liver cirrhosis, alcohol addicts without liver disease, and healthy controls.^{14,15} For several reasons—including fading interest in psychometric measures in favor of “more sophisticated

and objective” methods such as computer-aided EEG analysis and evoked potential studies—their data were not published until the end of the 1990s, and finally the test battery was published in 1999.¹⁶ Although the PSE-Syndrome-Test had been published in German exclusively it has been acknowledged worldwide, and by using an English translation provided by Hans Schomerus himself, clinicians all over the world undertook the task to elaborate norm data of the PHES for their respective population to be able to apply the test battery to their patients. Today norm data for the PHES—the sum score of the battery—exist for example in Italy, Spain, Poland, South Korea and Great Britain and are currently elaborated in several further countries especially in South America and Asia. But, the provision of norm data which is needed for any new population that shall be studied takes time and effort, and is not really honored by the scientific community. In addition the application of the battery and the evaluation of the test results take about 20 min in every single patient. Thus, there is the desire for more elegant, e.g. time-saving solutions. The “Inhibitory Control Test (ICT)” is the most recent candidate. It takes about 15 min, and is considered to be unaffected by age so far, if not by education.^{11,12,17} The ICT is a computer-based test of attention and inhibitory control that requires the tested person to press a response button if in a series of letters presented on the computer screen an x is followed by a y or a y is followed by an x (targets). The subjects are also required to withhold the response in case that a y is followed by another y or an x is followed by another x. These pairs of letters are called lures. People tend to respond also to the lures. Comparing the ICT results of 50 patients with liver cirrhosis to those of 50 healthy controls adjusted for age and education, Bajaj and co-workers showed that the ability to inhibit this response is reduced in cirrhotic patients.¹¹ Patients were subdivided into those with and without mHE according to their test results in either the Number Connection Test A (NCT A), or the Block Design Test (BDT) or the Digit Symbol Test (DST) from the Wechsler Adult Intelligence Scale (WAIS). For each of these tests results below 2 standard deviations from the mean of the healthy control group were considered abnormal. In contrast to former recommendations an abnormal result in one of the tests was considered sufficient for diagnosing mHE.¹⁸ Patients with mHE according to this definition responded to significantly more lures than those without mHE and controls. Considering the test results of the healthy controls >5 lures was defined as cut-off between normal and abnormal test performance. This cut-off gave a sensitivity and specificity of 90% for

the diagnosis of mHE using the classification according to the results in the NCT A, BDT or DST as reference standard. In their further studies upon the use of the ICT for diagnosing mHE Bajaj et al emphasized that the ICT had further advantages compared to standard psychometric tests: the test could be applied by medical assistants (a point that has some importance only in the USA, where clinicians are encouraged not to do psychometric testing by themselves but to ask psychologists for support), the test evaluation was done automatically, and the whole procedure took less time than the standard psychometric assessment of patients with cirrhosis performed at their institution, which took about 35 min.¹²

However, they also pointed out, that the ICT needed standardization and validation since norm data have not yet been elaborated.^{11,12}

Amodio and colleagues from Italy were the first who evaluated the ICT for diagnosing mHE besides the Bajaj group, so far.¹⁷ They undertook a comparison of the ICT results with the PHES. Like Bajaj et al they found a significantly increased number of lures in patients with cirrhosis compared to controls. However, they did not find a significant difference between patients with and without mHE diagnosed according to the PHES results. A difference between these two patient groups could be observed only when the number of lures had been adjusted by the individual target accuracy. They concluded that “The ICT is not useful for the diagnosis of mHE, unless adjusted by target accuracy. Testing inhibition (lures) does not seem to be superior to testing attention (target accuracy) for the detection of mHE”. Of note, the number of lures observed in the controls in both study centers involved in their paper (Center A: 12.9 ± 5.8 ; Center B: 8.5 ± 5.2) was far above that observed by Bajaj and co-workers (3 ± 2).

Now Taneja and co-workers made a similar attempt to compare the ICT results and the PHES for their use in diagnosing mHE in the Indian population.¹³ In their study the test battery providing the PHES is a little bit different from the usual battery as the Number Connection Test B was substituted by the Figure Connection Test.¹⁹ Similar to the study by Amodio et al the diagnosis of mHE was made based on the PHES. Like in the studies by Bajaj and co-workers patients with mHE responded to significantly more lures than patients without mHE and healthy controls. But, there was considerable overlap between the groups. In addition there was obviously a far higher variability in the healthy control group regarding the number of lures than in the data shown by Bajaj et al (11.3 ± 5.6 versus 3 ± 2). ROC analysis was applied to determine the cut-off for ICT lures for the diagnosis of mHE and was finally set at ≥ 14 lures. Applying this cut-off 32.6% of the healthy controls scored abnormal in the ICT, the use of 5 lures as cut-off as done by Bajaj et al would have classified

88.4% as abnormal. The sensitivity of the ICT was calculated being 78%, the specificity for diagnosing mHE 65.6%. In contrast to the PHES the lures in the ICT had no prognostic value. In conclusion—similar to Amodio et al¹⁷—Taneja et al did not judge the ICT being useful for diagnosing minimal HE due to liver cirrhosis.¹³

The three groups who evaluated the ICT for diagnosing mHE so far appear to be following different aims. Bajaj et al^{11,12} were looking for a means that would enable them to test for mHE without being dependent on the support of a psychologist, and that took less time than their battery applied so far. Of note this battery comprising the Number Connection Test A, and the Digit Symbol Test and Block Design Test from the Wechsler Adult Intelligence Scale (WAIS) has never been evaluated for its use in diagnosing mHE, nor has the cut-off between normal and abnormal results in this battery which was defined as a test result below 2 standard deviations from the mean of the healthy control group in at least one of the three tests.

In contrast, Amodio et al¹⁷ and Taneja et al¹³ aimed to evaluate the use of the ICT for diagnosing mHE compared to a test battery which they had validated for their special population before. This difference in aims might be one reason for the different results. While in the Italian and the Indian study the ICT proved to be less sensitive and specific for the diagnosis of mHE than the PHES, in the American study the ICT worked similar to a traditionally used battery comprising 3 paper-pencil-tests with unevaluated but probably low specificity for mHE.

However, there is another striking difference between the three studies. While the cirrhotic patients perform quite similar in the ICT the American healthy controls do significantly better than their Italian or Indian counterparts. This has been explained by differences in the familiarity with computer games without any proof. It might also be due to a selection bias concerning the controls. In any case the huge difference between the three control groups underlines the need to elaborate reliable and valid norm data for every single population that shall be examined by any psychometric measure. Both, Bajaj et al^{11,12} and Amodio et al¹⁷ did not find age effects upon the number of lures, while Amodio observed an impact of education in the control group and a learning effect in the patients. These observations underline the need for further evaluation of the ICT before it can be recommended for diagnosing mHE.

There is one additional point that should be considered for studies evaluating any test for diagnosing mHE. Today, we do not have a gold standard for making the diagnosis, and we will not have one in the future due to the theoretical construct of mHE. The studies described above defined their own “gold standards”—two used the PHES, the other a combination of NCT A, DST and BDT. Evaluation of any

method compared to another will only be able to retrieve if and to which extent the two methods cover the same cognitive domains. Considering the fact that mHE is characterized by deficits in more than one domain diagnosis of minimal HE should not be restricted to deficits in one domain such as attention for example.^{18,20,21} The PHES has been developed in acknowledgment of the different features of mHE, though it still does not cover all of them, e.g. sleep disturbances. While there is always a desire to find simple solutions for complex tasks future attempts to improve diagnosing of mHE should aim at maximum specificity and sensitivity in diagnosing brain dysfunction thereby considering all possible different features instead of aiming at an improvement in time management and economics.

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