MHE Testing in Real World Scenario

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Professional MHE awareness is high but when it comes to psychometric testing for MHE the real world scenario is characterized by hesitation and testing is offered only to selected cirrhosis patients. The hesitation is rooted in doubts about which tests to use, lack of knowledge about treatment benefits, and uncertainty about the tests' ability to identify patients who will benefit from anti-HE treatment. Thus, the majority of MHE patients do not receive the available efficient anti-HE treatment. This mini-review attempts to quell some of these doubts. (J CLIN EXP HEPATOL 2018;8:438–440)

Minimal Hepatic Encephalopathy (MHE) is a serious and frequent problem for many cirrhosis patients but still far from all cases of MHE are diagnosed and treated. The real world scenario is still characterized by hesitation and MHE testing (i.e. some sort of psychometry) is offered only to selected cirrhosis patients. While nearly half of hepatologists seem to engage in MHE testing only 10% systematically examine their cirrhosis populations.^{1–3} The hesitation is rooted in doubts about which tests to use, lack of knowledge about treatment benefits, and uncertainty about the tests' ability to identify patients who will benefit from anti-HE treatment.^{1,2} These doubts go hand in hand with structural arguments about prioritizing time and staff for the purpose (Figure 1).¹ Together, the effects of such factors deprive the majority of MHE patients of the available efficient anti-HE treatment. This unsatisfactory status needs to be improved by clarification of the doubts mentioned so that more patients in need get the treatment. The mainstay of the standard treatment remains the efficient, safe, and cheap drug lactulose, which may be supplemented with branched chain amino acids or rifaximin in difficult-to-treat cases.⁵ Diagnostic approaches and treatment decisions vary between continents, countries and centers.^{1–3} No strategy is universally more correct than the one validated in its target population.

CHOOSING A TEST FOR MHE

Regarding choice of MHE tests complete standardization is at present not possible and in view of the diversity of MHE patients perhaps not even desirable. The important effort is to engage in testing rather than awaiting standardization. Still, to be able to communicate and exchange the effects of the testing strategy, a common comparator test is important. The Portosystemic Hepatic Encephalopathy Score (PHES) is widely endorsed for this purpose.⁴ However, no test is a stand-alone: More than one dedicated test is usually necessary to explore the multi-domain cerebral deficits of MHE in order to provide a meaningful basis for treatment decisions. Dedicated psychometric tests include the PHES, the Continuous Reaction Time Test (CRT), the Inhibitory Control Task Test (ICT), The Critical Flicker Frequency Test (CFF), and spectral Electro Encephalography (EEG).⁴ Common to these, besides their requirement for special equipment and trained staff, is that they describe deficits in cerebral function that are not clinically recognizable and thereby live up to the requirements dictated by the definition of MHE.

It is a cause of worry that cirrhosis patients are not systematically tested and treated for MHE. It is a frequently presented obstacle that the dedicated tests are too specialized and resource-heavy.^{2,5} This leads to a quest for other and more easy-to-perform tests that approximate the sensitivity and specificity of the dedicated psychometric tests. Such an endeavor, despite its inherent methodological problems, may be worthwhile to pursue if it helps more patients be offered the proper treatment.

NON-SPECIALIZED MHE-TESTS

Non-specialized tests are point-of-care tests not requiring special equipment or specifically trained staff. At present they mainly include Quality of Life (QoL) indices, the Stroop EncephalApp and the newcomer animal naming test (ANT)⁶—although, even such tests require some staff

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Abbreviations: CFF: Critical Flicker Frequency Test; CRT: Continuous Reaction Time Test; EEG: Electro Encephalography; ICT: Inhibitory Control Task Test; MHE: Minimal Hepatic Encephalopathy; PHES: Portosystemic Hepatic Encephalopathy Score; TIPS: Transhepatic Intra-jugular Portosystemic Shunt

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Figure 1 Reasons not to offer MHE testing stated by hepatologists world wide. Adapted from [1].

preparation to give meaningful outcomes and they have not been validated in the hands of unexperienced staff.

QoL in MHE is of key interest because most MHE patients experience severe problems in their daily living. This makes it tempting to use QoL scores diagnostically for MHE although it is obvious that such problems are not specific to any disease or condition. Recently, a diagnostic score based on responses from the generic QoL questionnaire, Sickness Impact Profile (SIPCHE score), was suggested.⁷ The score is derived from 4 individual Sickness Impact Profile (SIP) statements, male sex and age (score > 0 = MHE). In the validation study the true MHE diagnosis was taken to be given by impairment in ≥ 2 of other non-specialized psychometric tests: number connection test A and B, digit symbol test, and block design test. It was found that the SIPCHE score cut off > -0.079 identified MHE (as defined by the indicated tests) with an 80% sensitivity. The diagnostic shortcoming is that QoL is non-specifically influenced by several factors other than MHE. The methodological problem is that the test was not validated against dedicated tests. The conceptual weakness is that the score does not give information on the brain function disturbances that define MHE and is therefore a surrogate score. Further, it is still unknown if SIPCHE is suitable as a follow up tool.

The Stroop EncephalApp is freely available from AppStore and is a digitalized version of the original Stroop test used to test mental stress resilience and was recently introduced as a tool for MHE diagnosis (Figure 1).⁸ The EncephalApp (OffTime + OnTime > 190) identified MHE with a 90% sensitivity using the same non-dedicated reference tests as mentioned above. Further, the test

results tended to improve in a small group of patients in whom hyponatremia was corrected, and it deteriorated in those who had a TIPS inserted.⁸ In a 2016 study, using the PHES as a reference test, the test sensitivity was >70%.⁹ Hence, the Stroop EncephalApp may have the potential to improve diagnostic rates in centers currently not undertaking MHE testing. However, neither proper norms nor comparisons of platforms (tablet vs. smartphone, apple vs. android) are so far available.

The ANT is new for MHE but is a long-standing test in general neuropsychiatry.¹⁰ It is an extremely simple test of semantic fluency that requires no equipment. The patient is asked to name as many animals as possible in 60 s. Campagna et al. recently reported that patients with liver cirrhosis able to name less than 10 animals had an 80% likelihood of also being classified as having MHE or worse by the PHES.⁶ This was true for 60% of those who managed to name less than 15 animals. The data suggest that ANT could be used as quick screening test to identify those in need for further MHE diagnostics, although further validation is warranted especially regarding the ANT's ability to detect a response to anti-MHE treatment.

WHICH PATIENTS SHOULD WE OFFER TESTING AND TREATMENT FOR MHE?

First, it is now evident that effective treatment of MHE is readily available. The 2016 meta-analysis finally concluded that lactulose improves MHE manifestations with a very low number of four of patients needed to treat to obtain the benefit. In the same way lactulose efficiently prevents recurrent episodes of clinically manifest HE (number

needed to treat seven).¹¹ Add-on interventions, e.g. with rifaximin even improve this effect. Further, it is now demonstrated in a randomized fashion that abnormal psychometry predicts a positive effect of anti-HE treatment, an effect not obtained in patients with normal psychometry.¹² Under the assumption that the non-specialized MHE tests to a reasonable degree reflect the psychometric test results, the conclusion thus is that all cirrhosis patients should be systematically and repeatedly tested with the locally preferred non-specialized test (if dedicated specialized tests are not available). The risks of missing or falsely diagnosing some MHE cases by non-specialized methods are likely more than outweighed by the high number of patients in need of treatment. Furthermore, initial familiarization with the non-specialized test may well lead to an interest in the dedicated and more extensively validated psychometric tests.

An alternative approach might be to jettison the psychometric testing and simply prescribe lactulose to all HE high-risk cirrhotics, e.g. older patients, patients treated with diuretics or Transhepatic Intrahepatic Portosystemic Shunt (TIPS), those with a history of falls; not least those with former HE episodes, and possibly active drivers with liver cirrhosis.^{13–15} After all, at least half of them will have MHE upon psychometric testing anyway.⁴ However, such an approach is not feasible because the effect of anti-MHE treatments is impossible to evaluate without some sort of diagnostic and follow-up test and because it is unethical to burden the large group of patients without MHE with financial costs and possible side effects. Basing the treatment decisions on a diagnostic test (specialized or not) is therefore, in our opinion, the only appropriate strategy.

The objections over time and staff used for MHE testing are evidently less powerful or even less legitimate when the non-specialized tests are taken into consideration (Figure 1). Such objections should not in themselves deprive the majority of MHE patients of available treatment in face of the clinical knowledge. What remains is to get started and to strengthen and detail our knowledge by accumulation of systematic data and motivating clinical trials.

CONFLICTS OF INTEREST

The authors have none to declare.

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