Review

Minimal hepatic encephalopathy

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Hepatic encephalopathy (HE) is a neuropsychiatric disorder that may accompany either acute or chronic liver disease. It is defined as a disturbance of central nervous system function due to hepatic insufficiency and includes a large spectrum of clinical manifestations such as decreased intellectual function, personality disorders, alterations in level of consciousness and neuromuscular dysfunctions.[1]

According to the consensus conference of the 11th World Congress of Gastroenterology, it can be classified into 3 major clinical types:

a. HE associated with acute liver failure.

b. HE associated with portal systemic bypass and no intrinsic hepatocellular disease.

c. HE associated with cirrhosis and portal hypertension/ or portalsystemic shunts.

This last type can be divided in 3 subtypes:

I. Episodic HE

II. Persistent HE

III. Minimal -or subclinical- HE (MHE)[2]

MHE is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects together with a normal neurological examination.[3]

The pathogenesis of MHE is not yet clear.

Subcortical alterations in the basal ganglia has been suggested as a possible anatomical site responsible for the subclinical changes of this entity.[4,5,6] The selective reduction in glucose consumption in the area of the cyngulate gyrus, a nucleus involved in the attention process, coupled with focal alterations of cerebral perfusion support this hypothesis.[7,8]

On the other hand, the relation of subclinical changes to protein metabolism and plasma amino acid imbalance, the reduction in cerebral blood flow and the improved response of neuropsychological tests after therapetuic manipulations which are applied in clinically overt HE, suggest the impact of the liver disease on brain function.[9,10,11]

The incidence of MHE is estimated to vary from 30% to 84% in apparently healthy, non-encephalopthic-cirrhotic patients, depending on the diagnostic criteria used.[12-16] This large variation reflects the variability and the large number of tests used and, on the other hand, is related to the composition of the tested population in each study, especially to the severity and the etiology of their cirrhosis.[17]

Although the diagnosis of symptomatic HE is a diagnosis of exclusion, based mainly on a careful global and neuropsychiatric examination, MHE is not a clinically evident entity and thus, for their detection, requires specific neuropsychological and neurophysiological examination.[18]

Since the beginning of the 1970's, more than 60 different diagnostic tests and 8 test batteries have been proposed and used for the diagnosis of MHE, which can be classified in four major groups.

1. PSYCHOMETRIC OR NEUROPSYCHOLOGICAL TESTS

Based on the hypothesis that "mental changes can precede overt neurological symptoms of HE", Zeegen *et al* in the early 1970's, first demonstrated an abnormal score in approximately one third of 39 apparently healthy cirrhotic patients previously operated for portal decompression, using the Reitan trail making tests.[19]

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Thereafter, neuropsychologists have designed and used more than 25 psychometric tests for the detection of MHE with most common neuropsychological finding an impairment of motor speed and accuracy, accompanied with deficits in visual perception, visuospatial orientation, visual construction, concentration, attention and memory while the verbal ability is preserved.[9,10,20-25] From all these psychometric examinations and according to the grade of their diagnostic accuracy, four can be considered as the most sensitive: I) the Number Connection Test (NCT), available in two versions, part A and part B, ii) The Digit. Symbol Test (DST), iii) the Block Design Test (BlDes) and iv) the Reaction Time to Light or Sound Test (RT).[9,10,12,13,20-24]

Although psychometric tests are characterized by high sensitivity and a simplicity in performance, their interpretation is not as easy as suggested because a number of factors can influence the overall score. A proposed correction using the adequate age normalized values, is not the solution to the problem, because the final result is also influenced by the grade of cirrhosis, the educational level and the cultural background of the examined population, as well as subject to the effect of repeated learning.[9,12-14,16,20,26-36] A history of alcohol abuse also induces a minor influence in MHE diagnosis, as reported by several investigators.[10,37-39]

Thus, to abolish this effect, the use of different test variants of equal difficulty has been suggested. Taking into account that a different domain of cognitive functioning is measured by each psychometric test (NCT measures cognitive motor abilities, SDT motor speed and accuracy, etc.) several authors have been proposed their use in combination (test batteries).[6,40,41] The proposed comparison, between different neuropsy-chological domains can be also a useful diagnostic approach for this form of HE.[6] But, despite the efforts and the progress, there is not yet a "gold standard" for the neuropsychological assessment of MHE. Although psychometric tests are characterized by high sensitivity, their specificity and their positive predictive value are low.[16]

The newly developed computerized psychometric tests, Posner test, Sternberg Paradigm appear to be very promissing tools, but experience is still limited.[38,42,43]

The statement of the Consensus conference of the 11th World Congress of Gastroenterology proposed that at least two of the following psychometric examinations should be used: NCT-A, NCT-B, BlDes, DST. A standardized test battery that include the NCT-A and -B, the line-tracing test, the serial-dotting test and the DST (PSE-Syndrome-Test) is recommended.[2]

2. ELECTROPHYSIOLOGICAL OR NEUROPHYSIOLOGICAL TESTS

Due to the disadvantages and the difficulties in interpretation of neuropsychological tests, the use of electrophysiological methods has been proposed as a more objective and specific method for the assessment of MHE.[14,29,33,42,43]

Although EEG is the most widely used neurophysiological diagnostic tool for the detection of clinically apparent HE, its diagnostic role in MHE is minor.[14] With a percentage of abnormal examinations ranging between 8%-35% among cirrhotics without overt HE, it is considered less sensitive than psychometric tests, and its changes are not specific, as in other metabolic encephalopathies.[9,10,14,29,44-46] Additionally, psychotropic agents can induce similar alterations. For diagnosis of MHE, an elevated percentage of this activity is necessary.[46] Quantitative and automated "spectral" EEG analysis is preferable to visual EEG analysis for the assessment of MHE, because it integrates the tracing and delineates the dominant signals.[14,47-49]

Apart from EEG, several investigators have used evoked potentials (EP) such as the P300 (P300 event-related potentials), the SSEP (somatosensory-evoked potentials), the BAEP (brain stem auditory-evoked potentials) and the VEP (visual-evoked potentials) with a reported rate of abnormal findings in cirrhotics without overt HE ranging between 14%-78%, 5%-34%, 0%-41% and 0%-63% respectively.[13, 14,16,29,45,50-57] With the exception of P300, their sensitivity is unsatisfactory compared to that of psychometric tests, and the specificity cannot be fully determined.[14,47,52]

Several parameters can be determined for the interpretation of their results, that are expressed as time (in milliseconds) to positive or negative deflections, including peaks and latencies. In clinical practice, EP are not widely used because of the need for sophisticated equipment and neuropohysiological knowledge.[57]

The P300 examination is an endogenous EP that is regarded as representing stimulus evaluation processes. In contrast to the conventional EPs, the response on P300 does not depend on the physical properties of the stimulus, but rather on the meaning of the stimulus to the patient. In this test, the response to two different stimuli, visual and acoustic, is measured and the patient is asked to identifity a predefined stimulus.[52] A

prolongation of the P300 latency to acoustic stimuli is observed in patients with MHE.[55]

The Consensus conference of the 11th World Congress of Gastroenterology proposed: "When it is possible, quantitative neurophysiologic tools (like EEG with mean dominant frequency, P300 auditory evoked potentials) should be used.[2]

3. NEUROIMAGING TESTS

Brain imaging provides no useful information for the assessment of MHE.

Computer tomography must be used only for differential diagnosis. Although cranial magnetic resonance imaging shows characteristic abnormalities in cirrhotic patients (symmetric pallidal hyperintensities in T_1-weighted images), these changes do not correlate with the grade of encephalopathy.

Proton magnetic resonance spectroscopy and positron emission tomography (PET) are two relatively new imaging methods and the experience in diagnosis of MHE with these is very limited.[8,58,59]

4. TEST OF CEREBRAL METABOLISM

There is a very little data about tests of cerebral metabolism in diagnosis of MHE.[60,61]

Clinical significance of M.H.E.

Impact on daily life: The significance of MHE diagnosis is still a subject of debate.[15,17,37] Several investigators have reported a negative influence on daily functioning.[24,37] Other studies suggest a possible relation between MHE and the subsequent development of episodes of overt HE.[16,20,62]

The reduction in the ability of these patients to carry out activities (driving a car, performing at work) probably reflects the neuropsychological deficits founded in MHE. It has been reported that a percentage of between 44% and 70% of cirrhotics with the diagnosis of MHE show an impairment in their ability to drive an automobile.[23,63] On the other hand, other investigations, did not revealed differences in quality of automobile driving between cirrhotics with MHE and healthy subjects.[64,65]

Quality of life: Patients with MHE experience a poor quality of life with serious difficulties in sleep, hobbies, recreation and deterioration of body care. The performance of SIP (Sickness Impact Profile) questionnaires showed highest scores on the areas of social interaction, alertness, emotional behavior, mobility, sleep/rest, home management and recreation and pastimes.[37,66,67] Sleep abnormalities are frequent in all cirrhotics and may be related to alterations of circardian function, or could reflect anxiety and depression as a result of living with chronic disease.[24,68]

The prognostic value of MHE: The clinical repercussions of detecting MHE are still unknown. A possible prognostic value of psychometric alterations in the subsequent development of overt HE and survival is suggested by several authors, but very few studies can confirm these statements.[69,70] Most of these have been limited to patients with advanced liver disease (portal systemic shunts, decompensated cirrhosis)[9,61], and the follow up time was very short: less than 12 months.[9,50,61] Only two long term follow up studies have confirmed that MHE is an independent risk factor for the development of HE.[71,72]

The predictive value of MHE on survival is also a subject of debate and the relationship between severity of liver disease and psychometric alterations is not yet clarified.[38,72,73]

Treatment

The therapeutic approach of MHE can be divided into 3 major branches:

1. Dietary manipulation/Protein restriction: Although a one-week total protein restriction showed a significant improvement in neuropsychological abnormalities in patients with portal-systemic shunt, the administration of animal, vegetable or mixed protein diet for seven days did not show a significant difference in psychometric tests and conventional EEG examination between three groups of postshunted cirrhotics.[9,35] In the above studies the number of patients was also very small, 5 and 8 respectively, and the reported results cannot be considered reliable. Thus, the role of diet, and consequently the role of protein restriction, in patients with MHE is still controversial. On the other hand, the treatment of MHE must focus on the improvement of quality in life and a total protein-free diet cannot be tolerated for a long time period.
2. Administration of Branched-Chain Amino Acids (BCAA): The administration of BCAA could be an alternative treatment modality to dietary manipulations in patients with MHE. Two studies have been performed for this reason, but neither showed a clear beneficial effect on daily functioning and quality of life. An occasional and moderate improvement was

observed in 7 out of 15 and 3 out of 12 psychometric tests respectively.[36,74]

The comparison between administration of BCAA and placebo did not show any statistical significant difference.[74]

3. Non-absorbable Disaccharides: Although the short-term administration of lactulose seemed to impvove the mental status of patients with MHE,[75] the results from long-term studies are not so encouraging.

   Thus, the daily long-term administration of lactulose in cirrhotics compared with administration of placebo and controlled with psychometric tests showed a significant improvement in the score of 3 out of 5 examinations, but the daily functioning of patients remained stable.[76] It is remarkable that almost 30% of the examined population dropped out in the above study.

   Comparison between long-term administration of lactulose and lactitol showed no significant difference, nor any improvement in the DST results.[77]

   On the other hand, the comparison between long-term administration of high (0.5 g/kg) and low (0.3 g/kg) dose of lactitol showed a significant improvement in venous ammonia levels in both groups, and also better results in NCT and DST for the patients in the high dose group. With an overall drop-out rate of more than 20%, subjective improvement in concentration was reported only in 20% of patients from the high dose group.[78]

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