Original Research Article

Minimal hepatic encephalopathy: prevalence and associated factors

Abstract :

Introduction: Minimal hepatic encephalopathy (EHM) is a frequent and severe complication of liver disease with a poor prognosis. It is responsible for an altered quality of life for patients. However, it is a poorly understood complication. There is no consensus on the diagnosis itself. Consequently, this pathology is under-diagnosed.
The main objective of this study is to determine the frequency of minimal hepatic encephalopathy (EHM) in cirrhotic patients who do not have clinical hepatic encephalopathy and to identify its risk factors.

Materials and Methods: This is a prospective study. 40 patients were included over a period of one year. A psychometric score of hepatic encephalopathy (PHES) composed of 5 tests was calculated. Any patient with a PHES score < -4 had an EHM.

Results: We recruited 40 patients. The study population was characterized by a slight male predominance (60%), the average age of the patients was 60.7 ± 11.8 years. The prevalence of EHM was 42.5% and varied according to the Child-Pugh class of the patients (Child A: 11.76%, Child B: 47.06% and Child C: 41.18%). Thrombocytopenia, hypoalbuminemia and elevated ASAT were found to be independent predictors of EHM in cirrhotic patients.

Conclusion**:** The Psychometric Hepatic Encephalopathy Score (PHES) has been shown to be useful for the diagnosis of EHM and can be applied both in the outpatient setting and at the patient's bed. The frequency of EHM in our study was 42.5%. Its independent risk factors can be used as a screening tool in cirrhotic patients. Larger studies should be encouraged.

Keywords: Cirrhosis - Minimal hepatic encephalopathy - Psychometric tests - Child & Pugh score.

Introduction:

Hepatic encephalopathy (HE) includes a wide range of neuropsychiatric manifestations, commonly encountered in patients with hepatic dysfunction, in the absence of other concomitant causes of cerebral infarction [1]. Minimal hepatic encephalopathy (MHE) corresponds to grade 0 on the West-Haven scale (table 1) also called subclinical or latent encephalopathy, MHE assumes a normal neurological clinical examination but with cognitive deficits that can be demonstrated by neuropsychological tests.

Liver cirrhosis is the leading cause of liver-related death worldwide. Better still, HE has been shown to be associated with high mortality rates, regardless of the severity of the underlying liver disease in the world [2].

The aim of this work is to determine the frequency of minimal hepatic encephalopathy in adult patients with cirrhosis who do not present with clinical hepatic encephalopathy and to identify its risk factors

Stage	Distinguishing features
0	No abnormality detected
1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition
2	lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, impaired performance of subtraction
3	somnolence to semistupor, but responsive to verbal stimuli, confusion, gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

Table1 : West-Haven criteria for the diagnosis of Hepatic encephalopathy

Materials and method:

This is a prospective study spread over a period of one year from November 2020 to November 2021 that included 40 patients aged 18 or over with cirrhosis. Excluded were patients with clinical hepatic encephalopathy (HE), patients with psychiatric and neurological diseases responsible for cognitive impairment, such as Alzheimer's disease, Parkinson's disease, patients currently on psychoactive medications , such as antidepressants, sedatives,

narcotics, barbiturates, patients with impaired visual acuity and dyslexic patients, patients with neoplasia of any organ as well as medical conditions severe enough to affect cognitive function, such as people with severe heart, lung or kidney disease.

For screening for minimal hepatic encephalopathy, the portosystemic encephalopathy syndrome (PSE) test was performed and the psychometric score for portosystemic encephalopathy (PHES) was calculated. This PSE test was chosen for the study in accordance with recent AASLD (The American Association for the Study of Liver Disease) guidelines because it is a well-studied and well-validated test that can be used in monocentric studies.

In our study, a version of the PSE test modified according to the recommendations of Dhiman et al [3] was used. This version consists of 5 tests: Number Connection Test A and B (NCT A/B), Line Tracing Test (LTT), Digit Symbol Test (DST), Serial Dotting Test (SDT) explained in the table 2 below:

Test :	Description :
Number Connection Test A (NCT-A)	The randomly scattered numbers must be linked together in series as quickly as possible.
Number Connection Test B (NCT-B)	Randomly scattered numbers and letters must be connected in alternating series (1-A-2-B...) as quickly as possible.
Line Tracing Test (LTT)	A given line is to be drawn as quickly as possible
Digit-Symbol Test (DST)	The patient receives a sheet of paper on which each number from 1 to 9 is associated with a symbol. Under each number, the patient must write the corresponding symbol in a given time.
Serial Dotting Test (SDT)	This is a paper containing 100 circles. The upper part has 20 circles for training purposes. Subjects are asked to put a dot in each of the 100 circles given on the sheet as quickly as possible, after being prepared by putting a dot in the top 20 circles of the sheet.

Table 2: the components of PSE score [3]

The results of the various PSE tests were reported and adapted to the age and level of education of the patients using the Spanish standardization (available on the site: http://www.redEH.org) which allowed us to have the PHES score expressed in points. Like the majority of studies, the PHES score threshold was set at -4 for MHE screening, in other words, any patient with a PHES score < -4 had minimal hepatic encephalopathy (MHE).

Results:

The average age of the patients included in the study is 60.7 ± 11.8 years with extremes of 31 and 82 years. The sex ratio M/F is 1.5. 40% of patients did not go beyond 5 years of schooling, while 60% were in school for more than 5 years. Regarding toxic habits, smoking is found in 30%, and alcohol consumption in 15% of cases.

All patients presented with decompensated cirrhosis in the form of an edemato-ascites syndrome in 24 patients (60%), gastrointestinal bleeding in 21 patients (53%), hepatocellular carcinoma in 6 patients (15%), hepatorenal syndrome in 2 patients (5%) and ascitic fluid infection in only one patient (3%). Regarding the biological values, the median values of hemoglobin and platelet count were respectively 10.1 [7.8-12.2] g/dl and 71.5 [56-126.5] × 103 elem/ mm3. Median albumin and international normalized ratio (INR) values were 28 [25-34] g/L and 1.4 [1.3-1.7], respectively. The median values of total bilirubin (BT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were respectively 14 [12, 3-26.3] mg/L, 20.5 [13-39.3] IU/L, 38[20-76] IU/L, 93.5 [66.3-156.8] IU/L and of 47 [24-88] IU/L. Anemia (hemoglobin < 10 g/dL) and thrombocytopenia (platelet count < 100 x 103 elem/mm3) were present in 48% and 78% of patients, respectively. 63% of patients had hypoalbuminemia (<30g/L), while 65% had a prolonged INR (>1.2). 43%, 18%, 45%, 28% and 45% of patients had an increase in total bilirubin, ALT, AST, ALP and GGT, respectively.

In addition, an esophagogastroduodenal fibroscopy (FOGD) was performed in all patients and objectified the presence in 26 patients (65%) of esophageal varices stage 1, 2 or 3. Regarding the severity of cirrhosis assessed by the Child-Pugh score, More than half of the patients were classified Child-Pugh B with a percentage of 52%.

The descriptive analysis of the various bedside psychometric tests of our patients is summarized in Table 3.

Test :	average	standard deviation
NCT-A : *(seconds)*	121,35	33,437
NCT-B : *(seconds)*	177,40	46,690
DST : (number of cases filled in 90sec)	12,80	5,422
SDT : *(seconds)*	92,75	20,186
LDT : *(seconds)*	95,95	23,821

Table 3: Assessment of PHES in the study population

Regarding the PHES score, 17 patients had a PHES score < -4, indicating minimal hepatic encephalopathy with a prevalence rate of 42.5%.

Regarding the descriptive analysis, there is a significant difference between patients with EHM and those who are not in terms of the following variables: AST increase (P= 0.049); Thrombocytopenia (P= 0.033); Hypoalbuminemia (P= 0.016), and MELD score (P=0.001). Regarding the severity of cirrhosis, there is a progressive increase in the frequency of EHM from 11.76% among Child Pugh class A patients to 47.06% and 41.7% among those in class B and C respectively. The difference was statistically significant with a P value = 0.033. In multivariate analysis, only 3 variables were found to have independent predictive value for EHM. These are: ↑ASAT (>1.5N), hypoalbuminemia (Albumin<30g/L) and thrombocytopenia (Plq<100,000elem/m3) as shown in Table 4.

Variable	OR	IC 95%
↑ASAT	0,461	0,199 - 1,065
Hypoalbuminemia	0,277	0,074 - 1,035
Thrombocytopenia	0,215	0,033 - 1,409
Child-Pugh	3,312	2,553 - 4,070
MELD	2,680	1,307 - 6,668

Table 4: Multivariate analysis of factors associated with EHM ***OR:*** Odds ratio; **IC:** confidence interval

Discussion:

Hepatic encephalopathy is a common and severe complication of liver disease, with an unfavorable prognosis. It is responsible for an alteration in the quality of life of patients and their families. However, this is a poorly understood complication. The diagnosis itself is not the subject of consensus, and this pathology is often under-diagnosed. Symptoms of overt hepatic encephalopathy are reported in approximately 30-45% of patients with hepatic cirrhosis and 10-50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS) [4].

Comment [I1]: Add more literature to support your findings.

Hepatic encephalopathy is subdivided into three types: episodic, persistent, and minimal, depending on the clinical presentation of the patient. Patients with episodic hepatic encephalopathy may have apparently normal cognitive function between episodes. Patients with persistent hepatic encephalopathy are never completely free of hepatic encephalopathy. Patients with minimal hepatic encephalopathy remain clinically asymptomatic. Clinical hepatic encephalopathy is usually recognized at the bedside, while minimal hepatic encephalopathy (MHE) often goes unnoticed. Indeed, the term subclinical hepatic encephalopathy was originally proposed to identify patients with subtle manifestations of hepatic encephalopathy that are difficult to recognize. This term highlights the need for additional tests to diagnose a degree of brain dysfunction that could not be detected by standard clinical examination. 30-45% of patients with cirrhosis develop a cluster of potentially reversible neurocognitive abnormalities across the HE spectrum [5].

A general approach to diagnosing EHM is based on the following steps [6]: Presence of a disease that can cause EHM, such as cirrhosis or the presence of a port shunt -systemic. Confirmation of a normal mental state on clinical examination. Besides a normal neurological exam, the test that has proven most useful for this purpose is the Mini-Mental State Examination (MMSE). Finally, if the clinical examination and the MMSE give normal results, the next step is to quantify any latent cognitive deficits using psychometric tests. There are neurophysiological tests and imaging techniques to complement them, but they are mostly used in experimental settings. There is no ideal test for diagnosing EHM. Since the early 1970s, more than 60 diagnostic tests have been proposed and used for the diagnosis of EHM [7]. These tests can be classified into three main groups: Psychometric or neuropsychological tests (which we performed in this study), electrophysiological or neurophysiological tests and Neuroimaging tests. Neuropsychological testing is an established methodology for

quantifying cognitive impairment due to various forms of encephalopathy. The main shortcoming of neuropsychological assessment is the need for a long and complex evaluation by an expert. To avoid this difficulty, many authors have reduced the evaluation to a limited number of tests; these are the short neuropsychological batteries. Unfortunately, there is no consensus on the number of tests to include or the level of impairment corresponding to an abnormal result.

The psychometric hepatic encephalopathy score (PHES) has been standardized and validated by Weissenborn and col [3]. This test consists of a series of psychometric tests and was designed specifically for the diagnosis of MHE. The PHES initially included 7 tests: the line tracing (LTT), serial dotting test (SDT), digit symbol test (DST), number connection test (NCT - A and B), the digit span test (DST) and the d- cancellation test. However, the desire for a shorter battery and the low sensitivity of some of the tests led to the introduction of the revised battery, sometimes also called the portosystemic encephalopathy (PSE) syndrome test, which includes the NCT A and B, LTT, SDT and DST (Figure 1 and 2). When interpreting the PHES test, it is important to consider the influence of age, gender, education, and cultural differences on test performance. This battery assesses many of the abnormalities seen in patients with EHM, including motor speed and accuracy, visuo-spatial orientation, visual perception, visual construction, attention, concentration, and to a lesser extent measure, memory. Appropriate use of these measures has provided a short, objective, and reliable way to assess EHM at the bedside.

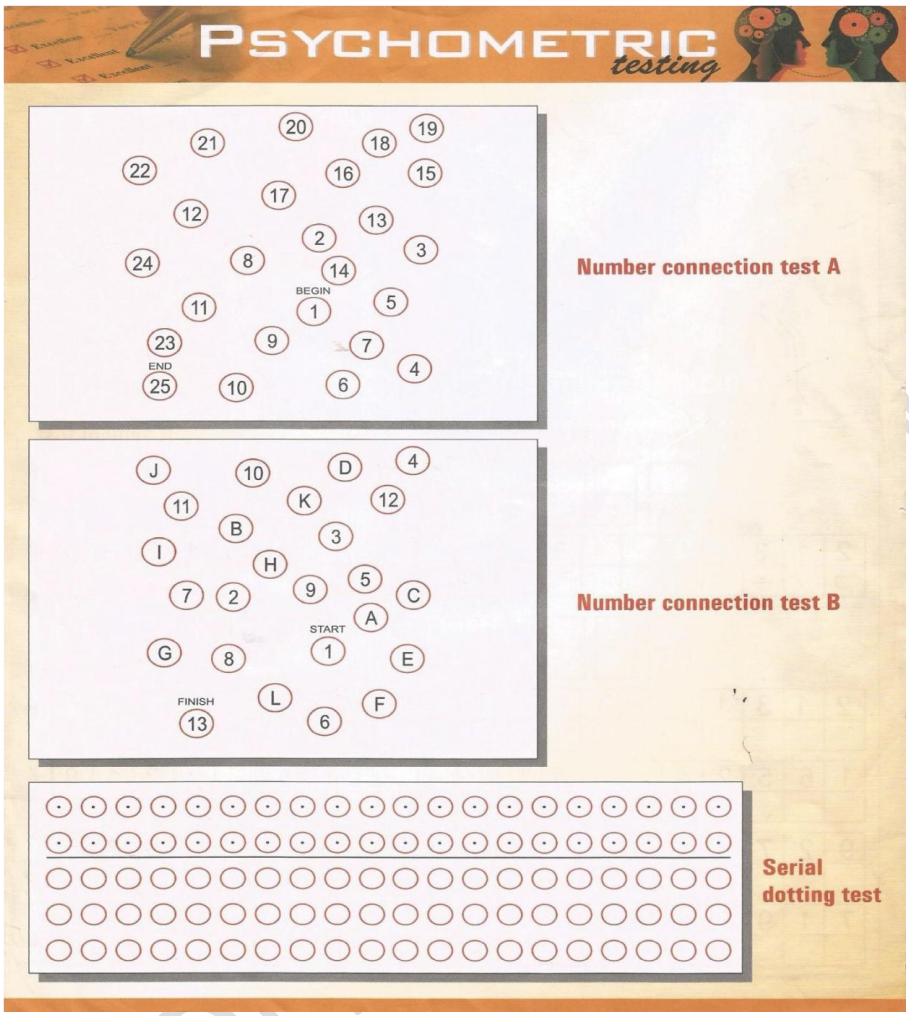

Figure 1: components of PHE : NCT-A, NCT- B et SDT: adapt by Weissenbom et al [24]

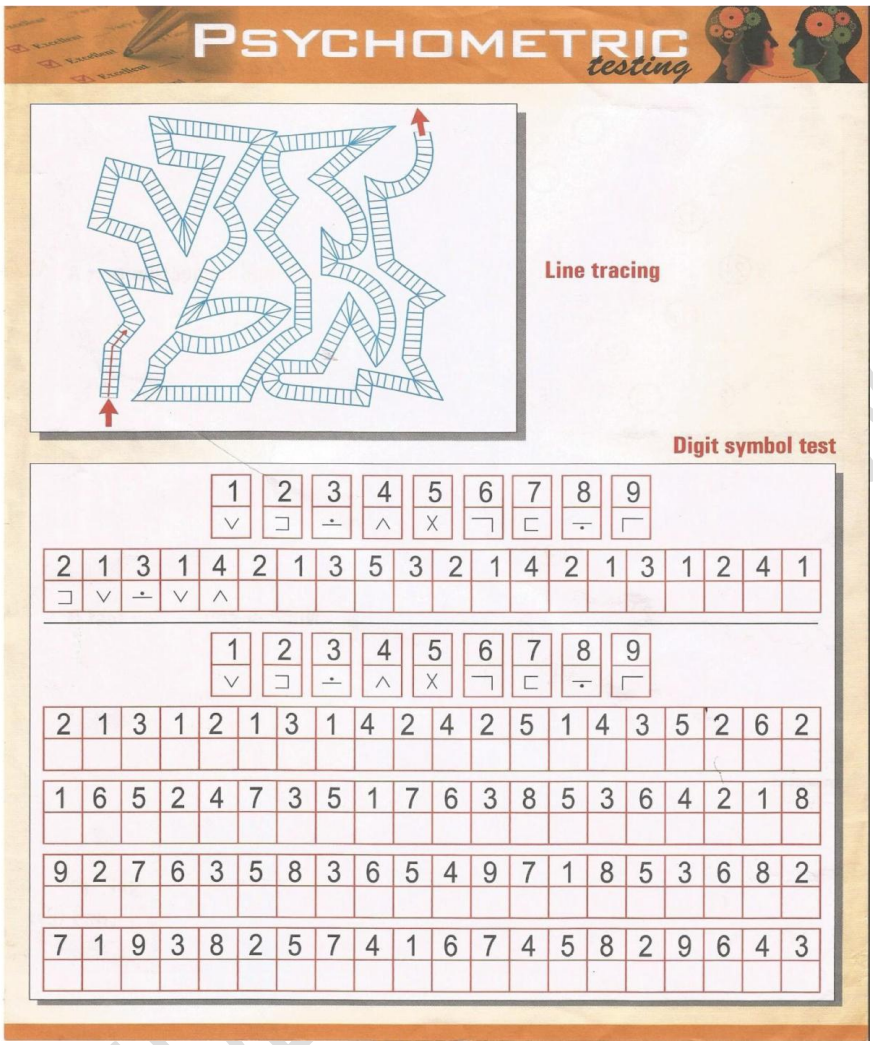

Figure 2: components of PHES (LTT et DST) : Adapt by Weissenbom et al [24]

Regarding the analytical results of our study, there was no significant difference in terms of sociodemographic factors between patients with EHM and those who are not. These results are consistent with several previous studies that found EHM to be unrelated to patient age, gender, or education level [8,9,10].

Among our 40 patients, 17 had a PHES score < -4, indicating minimal hepatic encephalopathy with a prevalence rate of 42.5%. This rate found in our study is consistent with that objectified in previous studies which showed a wide variation ranging from 35% to 75% (table 5) [8]. This variation is probably due to the divergence of the inclusion and exclusion

criteria taken into consideration, as well as the diversity of the tests used for the diagnosis [11].

study	date	country	Prevalence of l'EHM :	Tests used
Rathi et al. (12)	2019	India	59.7%	PHES
Bale A. et al. (13)	2017	India	52,2%	PHES
Li SW et al. (14)	2013	China	49.1%	PHES
Maldonado-Garza HJ et al. (15)	2011	Mexico	55.8%	PHES
Li YY et al. (16)	2004	China	50,9%	SDT, NCT-A
This study	2021	Morocco	42,5%	PHES

Table 5 : The prevalence of EHM according to different studies: *SDT: Serial Dotting Test NCT-A: Number Connection Test-A.*

Regarding the role of the Child Pugh score in screening for EHM, there seems to be disagreement in the literature [13]. While many studies have shown that cirrhotic patients with a Child Pugh B and C score have a higher prevalence of EHM compared to a Child Pugh A score [17,18,19] a few have not shown this difference [20, 21]. On the other hand, Das et al reported that although the prevalence of EHM was similar across Child and Pugh classes, the severity of EHM depended on the severity of the underlying liver disease [22]. In our study: a progressive increase in the frequency of EHM of 11.76% was objectified in patients with a Child Pugh A score and of 47.06% and 41.7% in patients with a B score and C of Child Pugh respectively. In univariate analysis, the score was associated with the presence of EHM (P = 0.033), however, in multivariate Child Pugh score is not an independent predictive value for EHM. Regarding the MELD score, its prediction of the EHM also remains controversial [19,21]. In our study and in nivariate analysis there was a significant difference between patients with EHM and those who are not according to the MELD score (P=0.001). This difference was not found in multivariate analysis.

A meta-analysis studying the development of hepatic encephalopathy (HE) in cirrhotic patients after TIPS (transjugular intrahepatic portosystemic shunt) showed that a high Child Pugh score was associated with an increased risk of HE while the score MELD failed to predict the same [23]. Yoo HY et al also investigated the relationship between MELD and HE

severity and found that MELD was not correlated with either HE severity or the presence of ascites [19]. Previous studies have shown that various factors such as the severity of liver disease, the presence of varicose veins [17,22] alcohol as the etiology [22], or even ammonia levels [23] were in favor of the onset of EHM in cirrhotic patients. Our study has objectified that only: ↑ASAT (>1.5N), hypoalbuminemia (Albumin<30g/L) and thrombocytopenia (Plq<100,000elem/m3) were associated with the appearance of EHM

Conclusion:

In view of the high prevalence of EHM and its rapid evolution, it would be desirable to apply to any cirrhotic patient simple psychometric tests such as the PHES to screen for EHM. Patients with Child-Pugh B/C cirrhosis presenting with thrombocytopenia, increased AST, and hypoalbuminemia should raise the clinician's suspicion of the presence of HME. Further studies are needed to determine the frequency of minimal hepatic encephalopathy in cirrhotics hospitalized in other departments in Morocco and Africa. This will allow both to validate the results of this study and to obtain a large database on the population.

Comment [I2]: Summarise your key findings here.

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