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Assessment of Minimal Hepatic Encephalopathy with Brain MRI and EncephalApp Stroop Test

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ABSTRACT

Background: *Minimal hepatic encephalopathy (MHE) consists of subtle cognitive deficits that are not apparent on a standard neurological examination. Minimal hepatic encephalopathy has been reported in up to 80% of cirrhotic patients and is associated with decreased job performance, poor driving performance, impaired quality of life, and poor survival. In parallel, brain magnetic resonance imaging (MRI) abnormalities are known to occur in liver cirrhotic patients in the form of T1 globus pallidus hyperintensities. In recent years, a new psychometric test for diagnosing MHE has been developed as an app for smartphones and tablets (EncephalApp Stroop test). A translated version of the app is available in Romanian language.*

Aim: *To use EncephalApp Stroop test for MHE diagnosis in our cirrhotic patients; to describe the main brain MRI abnormalities encountered in these patients; and to establish if Stroop test results correlate with imaging findings, clinical neurologic findings, and liver function parameters or prognosis.*

Material and methods: *Cross-sectional study over a one-year period, involving 30 adult patients with liver cirrhosis. Subjects were evaluated through a standard neurological examination, psychometric testing using EncephalApp Stroop test, electroencephalogram and brain MRI. In parallel, 40 adult healthy controls were also recruited and evaluated with the EncephalApp Stroop test using the same methodology.*

Results: *Age distribution was similar between the two groups ($p=0.6$). The mean age of patients was 50±10 years and that of controls 51±12 years. Mean Stroop result was 171±26 seconds for the patient group and 143±20 seconds for the control group ($p<0.0001$). There was a direct correlation between Stroop test results and age in the control group ($R=0.69$, $p<0.0001$) but not also in the patient group ($R=0.28$, $p=0.13$). Statistically significant results were obtained by using the Fischer exact test for both cut-off values: 145 seconds in patients < 45-year-old ($p<0.001$) and 190 seconds in those ≥ 45 years-old ($p=0.03$). MRI T1-hyperintensities of the basal ganglia, blood ammonia levels and electroencephalographic changes were not associated with poorer results.*

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Conclusions: *Our pilot study, although small, confirmed that patients with liver cirrhosis may have subtle deficits in cognitive areas like attention, concentration or reaction time. This can be assessed easily with the EncephalApp Stroop test which is readily available for use on smartphones or tablets.*

Keywords: minimal hepatic encephalopathy, EncephalApp Stroop test, liver cirrhosis.

ABBREVIATIONS (in alphabetical order)

CT: Computer tomography
DLPFC: Dorso-lateral pre-frontal cortex
EEG: Electroencephalogram
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HDV: Hepatitis D virus
HE: Hepatic encephalopathy
INR: International normalized ratio
MELD: Model for end-stage liver disease
MHE: Minimal hepatic encephalopathy
MMSE: Mini-mental state examination
MRI: Magnetic resonance imaging
PHES: Psychometric hepatic encephalopathy score
USA: United States of America

BACKGROUND AND AIMS

Brain magnetic resonance imaging (MRI) abnormalities are known to occur in liver cirrhosis, usually in the form of globus pallidus T1-hyperintensities (1). These are due to increased levels of serum manganese in cirrhotic patients, with subsequent manganese accumulation in the basal ganglia (2). The clinical relevance of these brain MRI findings has been questioned by several authors, who have failed to correlate these abnormalities with neurological dysfunction, severity of liver failure, serum ammonia levels, EEG abnormalities or psychometric test results (1, 3, 4). Conversely, other authors have established a significant correlation between the degree of T1 signal intensity and Child-Pugh scores, prior episodes of hepatic encephalopathy, presence of postural tremor, or prothrombin activity (5). Thus, the issue regarding the clinical relevance of these brain MRI findings is not settled yet. It has been established that those brain MRI changes would disappear after successful liver transplantation (1,5).

Up to 80% of cirrhotic patients can develop subclinical or minimal hepatic encephalopathy (MHE) (6), characterized by subtle cognitive deficits that are not clinically apparent on a standard neurological examination, but identifiable through psychometric testing (7).

Given the asymptomatic nature of MHE, physicians tend to overlook its diagnosis. However, the presence of MHE has been associated with an impaired quality of life and job performance (6, 8, 9), being a major cause of premature retiring in cirrhotic patients (8). Minimal hepatic encephalopathy is also associated with poor driving performance (10) and is an independent risk factor for poor survival (11).

Numerous psychometric and neurophysiologic tests have been developed for the diagnosis of MHE, each with its own advantages and drawbacks. Current guidelines recommend the use of psychometric hepatic encephalopathy score (PHES) or repeatable battery for the assessment of neuropsychological status (RBANS) (12-13).

In recent years, a new psychometric test for the detection of MHE, EncephalApp Stroop test, has been developed as an app for smartphones and tablets. It relies on the Stroop effect and has been validates so far in the USA for diagnosing MHE (14-15). The above-mentioned app has been proved to have good face validity, test-retest reliability and external validity. The authors established a cut-off value for MHE diagnosis of $\geq$ 145 seconds for patients aged under 45 and $>$ 190 seconds for those $\geq$ 45 years (15). Because test results can be influenced if used on patients whose native language is different than English, a translated version of the test has been developed in Romanian (with authors' approval).

The EncephalApp Stroop test consists of two states, termed Stroop Off and Stroop On. In the Stroop Off state, the patient has to select (as fast as possible) the color which is seen as a string of four hash signs (####). When the Stroop effect is activated (Stroop On), the patient has to select (as fast as possible) the color used to write down another color word. There are five tests with

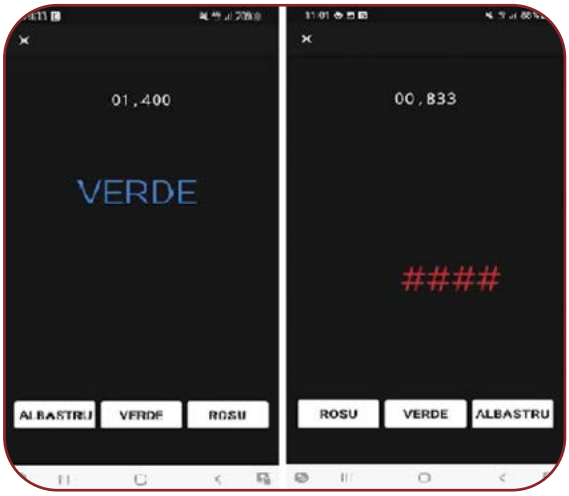

FIGURE 1. (A) A typical example of a Stroop effect (Stroop On), in which the patient has to select the color used to spell another color word; in this case, the right answer would be "Blue" (in Romanian "Albastru"); (B) Conversely, in the Stroop Off state, the patient just has to select the color seen; in this example, the right answer would be "Red" (in Romanian "Roşu")

Stroop Off and five tests with Stroop On, each test consisting of ten consecutive elements (strings of hash signs or color words). The patient is timed and asked to complete all ten tests as fast as possible. The total time is noted as Stroop Off (for the five tests with Stroop Off), Stroop On (for the five tests with Stroop On) and Stroop Off + On (when added together) (see Figure 1).

Objectives

Based on the above-mentioned considerations, we set the following objectives: 1) to describe the main brain MRI abnormalities encountered in our cirrhotic patients; 2) to use EncephalApp Stroop test for MHE diagnosis in these patients; and 3) to establish if Stroop test results correlate with imaging findings, clinical neurologic findings, liver function parameters or prognosis. ❑

MATERIAL AND METHODS

We recruited 30 adult patients diagnosed with liver cirrhosis at the Gastroenterology and Hepatology Department of Fundeni Clinical Institute, Bucharest, Romania, over a one-year period (August 2016 – July 2017). All patients were awaiting liver transplantation and have been evaluated through standard neurological exam and EEG prior to inclusion on the waiting list.

Periodic assessment of liver function and portal hypertension was performed through abdominal ultrasound, upper digestive endoscopy, laboratory tests, abdominal CT scan and/or abdominal MRI. Blood analysis included complete blood count, serum albumin, total serum protein, fibrinogen, INR, prothrombin time, aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, conjugated bilirubin, urea, creatinine, uric acid, glycemia, lipid profile, serum sodium, serum potassium and venous ammonia. The severity of liver function was measured by using the MELD and Child-Pugh scores.

In addition to this standard assessment, each patient was evaluated through brain imaging (on a 1.5 Tesla MRI) and psychometric testing. Brain imaging protocol included T1/T2, T1SE, T2 FLAIR, DWI, SWI, 2D-TOF and 3D-TOF. Of the psychometric tests available for MHE, we used EncephalApp Stroop test. Each patient met the inclusion and exclusion criteria (Table 1) and was trained according to the original recommendation prior to evaluation. Testing occurred on an Apple iPad Mini 4, with the patient seated at a table in a quiet, airy and bright room. Emphasis was placed on factors that might influence the patient's concentration during testing (*e.g.*, lack of sleep, hunger, thirst, urination/defecation needs, use of glasses).

The diagnosis of MHE was based on currently available cut-off values of ≥ 145 seconds for patients under 45 and > 190 seconds for those ≥ 45 years.

TABLE 1. Inclusion and exclusion criteria for EncephalApp Stroop test

Exclusion criteria	Inclusion criteria
Major neuro-psychiatric comorbidities	Age ≥ 18-years-old
Use of psycho-active medication	Liver cirrhosis ± prior history of overt HE
MMSE < 25 points	
Color blindness	
Uncorrected refractive errors	
Lack of reading abilities	
Suicide attempt in the last three months	
Alcoholic coma	
Overt hepatic encephalopathy	

In parallel, 40 adult controls without liver cirrhosis were recruited after meeting the same exclusion criteria as subjects selected in the patient group and further tested under similar conditions. The purpose of that approach was (1) to compare the results between the two groups (patients *versus* controls), thus confirming or establishing new cut-off values for MHE diagnosis, and (2) to relate the results to brain MRI abnormalities.

All patients signed an informed consent form and voluntarily participated in this study. Patients' medical information (discharge papers, laboratory results) was accessed using the hospital's informatic system Hipocrate. Patient database was created with Microsoft Office 365 and statistical analysis was done with MedCalc Statistical Software version 18.9. The study protocol was approved by the Ethics Committee of Fundeni Clinical Institute. ❑

RESULTS

There were 76.6% males (n=23) in the patient group, while in the control group there was a female predominance of 75% (n=30). Age distribution was similar and did not vary statistically between the two groups (p=0.6). The age of patients ranged between 28-65 years (mean age 50±10 years), and that of control subjects between 27-68 years (mean age 51±12 years). The most common liver cirrhosis etiologies included chronic liver disease due to hepatitis B virus ± hepatitis D virus (43.3%, n=13), followed by chronic liver disease due to hepatitis C virus (23.3%, n=7) and alcoholic liver disease (20%, n=6) (Table 2).

TABLE 2. List of cirrhosis etiologies in the patient group

Etiology	Number of patients
Hepatitis B ± D viruses	13
Hepatitis C virus	7
Alcoholic liver disease	6
Primary biliary cirrhosis	2
Autoimmune hepatitis	1
Toxic (drug-induced)	1

TABLE 3. Liver disease severity based on etiology

Etiology	MELD score		Child-Pugh score	
HBV ± HDV	16 ± 5	p=0.3	8 ± 2	p=0.07
Alcoholic liver disease	13 ± 3		7 ± 1	
HCV	17 ± 3		9 ± 1	

Disease duration between diagnosis of cirrhosis and brain imaging assessment varied between 0–20 years (mean duration 5 ± 5 years); MELD scores varied between 6–22 (mean 15 ± 5) and Child-Pugh scores between 5–11 (mean 8 ± 2). There were no significant differences in liver disease severity (measured by the MELD and Child-Pugh scores) between cirrhosis etiologies (Table 3).

Liver disease severity among the remaining four patients was as follows: MELD=11 and Child-Pugh=A6 for the patient with autoimmune hepatitis, MELD=8 and Child-Pugh=A5 for the first patient with primary biliary cirrhosis, MELD=11 and Child-Pugh=A7 for the second patient with primary biliary cirrhosis, and MELD=10 and Child-Pugh=A6 for the patient with drug-induced cirrhosis. Prior history of episodic HE was present in 30% (n=9) of patients.

There was a direct correlation between Stroop test results and age in the control group (R=0.69, p<0.0001) (Figure 2), which was to be expected, given that certain functions like concentration or reaction time would diminish with advancing age. However, no such correlation was found in the cirrhotic group (R=0.28, p=0.13) (Figure 3). Gender-related results (between males and females) did not vary significantly in either the control (p=0.9) or patient group (p=0.6). The mean Stroop test results were 143±22 seconds for males and 144±19 seconds for females in the control group, and 173±29 seconds for males and 167±8 seconds for females in the patient group.

Stroop test results varied significantly between the two groups as a whole (p<0.0001). The mean Stroop result (Off + On) was 171±26 seconds for the patient group and 143±20 seconds for the control group (Figure 4). There were seven patients aged under 45 years who scored ≥145 seconds (100%), thus surpassing the cut-off value for MHE. Conversely, only one of the 14 controls aged under 45 scored ≥145 seconds (7%). In the patient group, four (17.4%) of those aged ≥45 years (n=23) scored >190 seconds, while in the control group none (0%) of those aged ≥45 (n=29) scored >190 se-

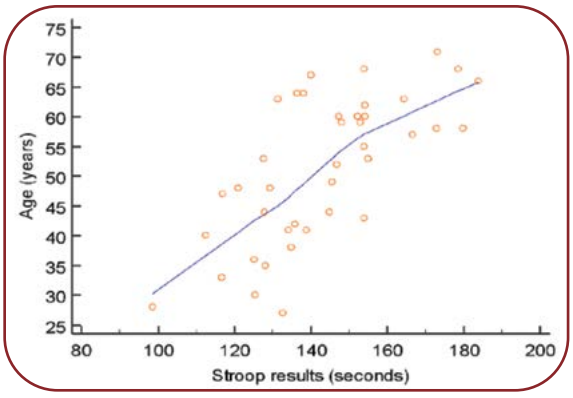

FIGURE 2. The relation between Stroop test results and age in the control group

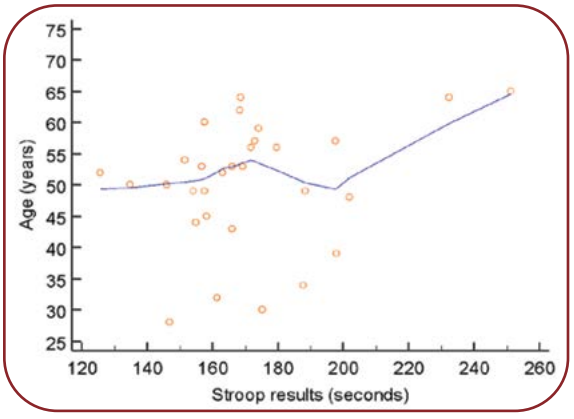

FIGURE 3. The relation between Stroop test results and age in the patient group

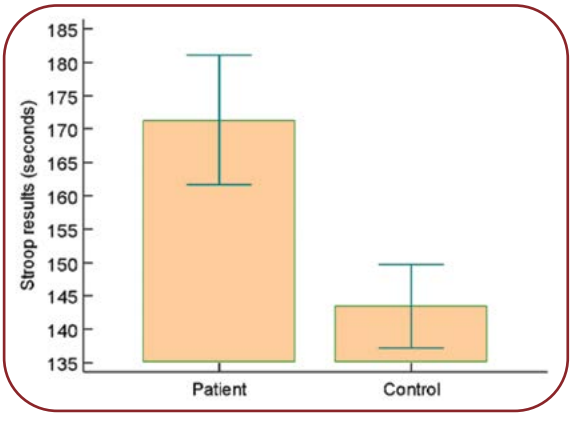

FIGURE 4. Comparison of Stroop test results between the patient and control groups

conds. Statistically significant results were obtained by using the Fischer exact test for both cut-off values: 145 seconds in patients aged <45 (p<0.001) and 190 seconds in those aged ≥45 years (p=0.03) (Figures 5 & 6).

Stroop test results did not correlate with liver disease severity as measured by the MELD

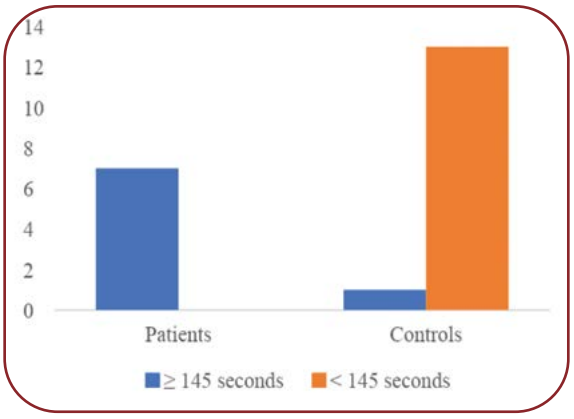

FIGURE 5. Comparison of Stroop test results in subjects aged < 45 years

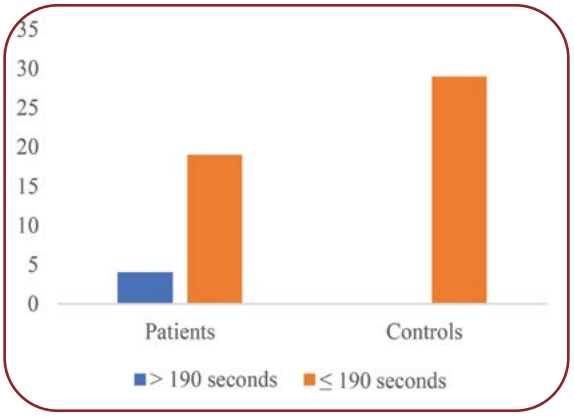

FIGURE 6. Comparison of Stroop test results in subjects aged ≥ 45 years

(R=-0.1, p=0.6) and Child-Pugh scores (R=-0.05, p=0.8). No correlation was found between Stroop test results and other laboratory parameters such as hemoglobin level (R=-0.02, p=0.9), total bilirubin level (R=-0.16, p=0.4), platelet count (R=0.27, p=0.14) or blood ammonia levels (R=0.2, p=0.3). Stroop results did not vary significantly between patients with prior episodes of hepatic encephalopathy and those without them (p=0.9).

T1-hyperintensities involving the globus pallidus were seen in 83.3% (n=25) of patients, while in 13.3% (n=4) the abnormalities extended to the cerebral peduncles. Five patients (16.6%) did not present T1-hyperintensities (Figure 7). On Stroop test evaluation, no difference was noted between patients with or without globus pallidus T1 hyperintensities (p=0.5).

Atrophic changes of the brain were described in 40% (n=12) of patients, although in the majority of cases the atrophy was qualitatively de-

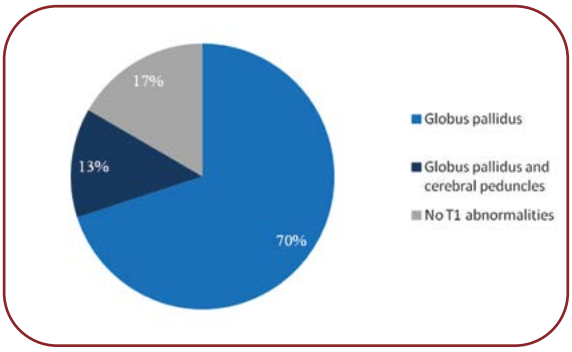

FIGURE 7. Prevalence of T1 hyperintensities in our cirrhotic patients

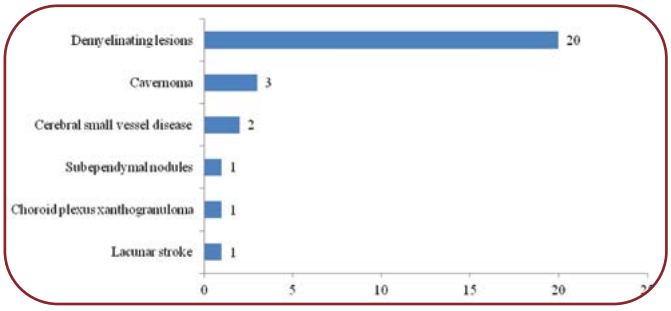

FIGURE 8. Prevalence of other brain MRI findings in our cirrhotic patients

scribed by the radiologist as discrete or small. No brain MRI was previously performed in these patients in order to dynamically assess the degree of atrophy. There was no significant age difference between patients with atrophic changes and those without them (p=0.37). Stroop test results were not influenced by the presence of these atrophic changes (p=0.7). There was a high prevalence of non-specific subcortical demyelinating lesions (66%, n=20). Other brain MRI findings described were cavernomas (n=3), cerebral small vessel disease (n=2), lacunar stroke (n=1), choroid plexus xanthogranuloma (n=1) and subependymal nodules (n=1) (Figure 8).

Of interest, electroencephalographic changes suggestive of metabolic encephalopathy were present in 50% (n=15) of patients in the form of slow wave activity (n=7) and/or spike-wave complexes (n=11). These changes are suggestive of subclinical encephalopathy in a patient with normal neurological examination. However, in our patients, Stroop test results were not significantly different between those with and without EEG findings (p=0.34). ❑

DISCUSSIONS

The Stroop effect is a neuropsychological tool which evaluates the ability of an individual to inhibit cognitive interference (*i.e.*, when processing a stimulus affects the simultaneous processing of another stimulus) (16). In our case, it is the tendency to experience difficulty when naming a physical colour that is used to spell the name of a different colour (17).

When encountering two contradictory stimuli of which only one must be chosen, there will be a slowing of reaction time, because the intentional reaction must overcome the automatic reaction (which is carried out more rapidly and without intention) (18). Regarding the specific brain locus involved in the Stroop effect, a paper published in 2019 (19) highlighted a possible cascade of control, comprising of the posterior DLPFC – mid-DLPFC – caudal mid-cingulate – rostral dorsal anterior cingulate cortex – feedback to DLPFC. The posterior DLPFC biases towards sensory or perceptual information. The mid-DLPFC selects the information to be maintained in the working memory. Next, the caudal mid-cingulate is involved in late-stage response selection, resolving the competition between potential responses. Finally, the rostral anterior cingulate cortex is involved in response evaluation and sends information back to the DLPFC for adjustment.

The evidence of altered glymphatic clearance in some areas of the brain (prefrontal cortex, olfactory bulb and hippocampus) was demonstrated in an animal model of chronic liver disease with hepatic encephalopathy (20). The alteration of glymphatic clearance may lead to accumulation of waste products in the interstitial fluid of the brain (for example in the prefrontal cortex) and thus may contribute to the development of cognitive impairment and, subsequently, to poorer test results on psychometric testing.

EncephalApp Stroop test was first validated in American patients in an article published in 2013 (14). The authors established a cut-off value of >274.9 seconds for the detection of MHE in patients with liver cirrhosis and showed that the results correlated with the MELD score and were worse in subjects with prior overt hepatic encephalopathy. In a subsequent article published in 2014, Bajaj *et al* established new age-related cut-off values for the diagnosis of MHE, that was ≥145 seconds for subjects aged under 45 and >190 seconds for those aged ≥45 (15). In the following years, authors from other countries published their experience with EncephalApp Stroop test in diagnosing MHE.

Zeng *et al* compared the results of the App with those of the PHES (used as gold standard) in Chinese patients and concluded that a cut-off value of 186.63 seconds had the highest sensitivity (86%), but an unsatisfactory specificity (59%) (21). In their study, both age and alcoholic hepatitis were positively correlated with the risk of MHE. Another article published by Luo *et al* described a sensitivity of 84.6% and a specificity of 74.4% when using EncephalApp Stroop test (and comparing the results with

the PHES results) (22). In a subsequent paper, the same first author highlighted that the total time scored on the Stroop test was also an independent predictor for poor sleep quality in patients with MHE (23).

Similar to our research, Cunha-Silva *et al* validated the EncephalApp Stroop test in Brazilian patients (24). They established a cut-off value of >269.8 seconds as having good sensitivity (87%) and specificity (77%), and pointed out that there was no influence of gender, age, education and familiarity with smartphones in the test results. The App was also validated in South Korean patients by Yoon *et al*, who analyzed the accuracy of adjusted psychomotor speed ("rate correct scores", which were both age- and sex-related). They concluded that both the Stroop test and the rate correct scores showed significant differences between healthy subjects, cirrhotic patients without MHE and cirrhotic patients with MHE (25).

In a multicenter study, Allampti *et al* showed that EncephalApp Stroop test had a good sensitivity in diagnosing MHE as well as a predictive capability (independent of the MELD score) of overt HE development (26). This was further confirmed by Duarte-Rojo *et al*, who noted that testing with either PHES, Stroop test, or the combination PHES + Stroop test was equivalent to diagnose MHE and to predict overt HE development (27). ❑

CONCLUSIONS

Our pilot study, although small, confirmed that patients with liver cirrhosis may have subtle deficits in cognitive areas, including attention, concentration or reaction time. This was demonstrated by poorer results on EncephalApp Stroop test as compared with normal healthy controls. Of interest, Stroop test results directly correlated with age in the control group (which was expected by us), but not also in the patient group. This may reflect the uniform alteration of cognitive function in MHE subjects, irrespective of age. Age-related cut-off values were used to differentiate between cirrhotic patients with and without MHE. The results were statistically significant when compared with the control group.

However, Stroop test results were not correlated with liver disease severity or other paraclinical parameters. In particular, brain MRI T1-hyperintensities involving the basal ganglia, blood ammonia levels and electroencephalographic changes were not associated with poorer results. The biggest limitation of our study is its very small size; therefore, future studies will be needed to establish better correlations between Stroop results and other parameters, in order to properly define subclinical hepatic encephalopathy. ❑

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