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PERI-LIVER TRANSPLANT NEUROLOGICAL MANIFESTATIONS: INCIDENCE, CLASSIFICATION, RISK FACTORS, DIAGNOSTIC EVALUATION AND PROGNOSIS

PHD THESIS SUMMARY

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List of published scientific works

1. **IC Lupescu**, S Iacob, C Pietrareanu, L Gheorghe. Assessment of excessive daytime sleepiness in cirrhotic patients. *Ro J Neurol*. 2022; 21(4):306-310. https://doi.org/10.37897/RJN.2022.4.4 (Capitolul 6).

2. **IC Lupescu**, MS Iacob, L Gheorghe. Is measuring serum ammonia helpful in patients with liver cirrhosis?. *Ro Med J*. 2023; 70(1):39-42. https://doi.org/10.37897/RMJ.2023.1.7 (Capitolul 7).

3. **IC LUPESCU**, S IACOB, IG LUPESCU, C PIETRAREANU, L GHEORGHE. Assessment of Minimal Hepatic Encephalopathy with Brain MRI and EncephalApp Stroop Test. *MAEDICA – a Journal of Clinical Medicine*. 2023; 18(1):4-11. https://doi.org/10.26574/maedica.2023.18.4.4 (Capitolul 5).

4. **IC Lupescu**, S Iacob, C Pietrareanu, L Gheorghe. Validation of EncephalApp Stroop Test for diagnosing minimal hepatic encephalopathy in the Romanian population. To be published in *J Gastrointestin Liver Dis*. 2023 Impact factor: 2.1. (Capitolul 5).

5. **IC Lupescu**, S Iacob, N Lupascu, IG Lupescu, C Pietrareanu, L Gheorghe. The Prevalence of Cerebral Aneurysms in Patients with Polycystic Liver Disease. *Rom J Mil Med*. 2023; 126(3):317-321. https://doi.org/10.55453/rjmm.2023.126.3.12 (Capitolul 8).

6. **IC Lupescu**, S Iacob, IG Lupescu, L Gheorghe, AO Dulamea. From cirrhosis to paraparesis. *Ro J Neurol*. 2019; 18(4):211-214. https://doi.org/10.37897/RJN.2019.4.9 (Capitolul 7).

7. **IC Lupescu**, IG Lupescu, R Cerban, L Gheorghe, D Anghel. An arachnoid cyst you don't see every day. *Ro J Neurol*. 2021; 20(1):115-117. http://doi.org/10.37897/RJN.2021.1.16 (Capitolul 7).

INTRODUCTION

The research topic of this paper is based on two motivations. On one hand, the interdisciplinary nature of the subject (given the impact of liver pathology on the nervous system), and on the other hand, the excellent collaboration I had with the team of the Gastroenterology and Hepatology Department. Of course, there is also the privilege of conducting my activity in a liver transplant center (the first center of its kind in Romania).

Although the neurological complications of liver cirrhosis and liver transplantation do not constitute a new research topic per se, we tried to share our own experience in the field and to contribute in this way to the advancement of knowledge. We addressed a few topics of interest, such as the diagnosis of minimal hepatic encephalopathy, or its association with the risk of developing post-liver transplant neurological complications.

The main advantage of this paper is the interdisciplinary approach to the subject, since the clinical and paraclinical findings were studied both from a neurological and from a gastroenterological point of view, and the gastroenterological data were correlated with the neurological ones.

Through this work, we aim to lay the foundations for a good practice guide for the diagnosis of neurological complications associated with liver cirrhosis and liver transplantation.

Under the term “neurological complications of liver cirrhosis”, we refer first of all to hepatic encephalopathy. However, patients with liver cirrhosis are predisposed to develop other neurological conditions, of which we mention acquired hepato-cerebral degeneration, hepatic myelopathy, central nervous system infections and intracranial hemorrhages [1].

Polycystic liver disease should also be mentioned as a particular entity, the risk of its association with cerebral aneurysms and, implicitly, the risk of subarachnoid hemorrhage through their rupture, being discussed here.

I. GENERAL PART

1. HEPATIC ENCEPHALOPATHY

The general part consists of a review of the main neurological manifestations encountered in patients with liver cirrhosis awaiting liver transplantation (pre-transplant neurological manifestations), as well as in liver transplanted cirrhotic patients (post-transplant neurological manifestations).

We started by characterizing hepatic encephalopathy (HE) and minimal hepatic encephalopathy (MHE) from the viewpoint of classification, epidemiology and clinical picture. Subsequently, we listed and described the main paraclinical investigations that we have at our disposal for the assessment of hepatic encephalopathy.

1.1. CLASIFICATION

Depending on the severity of the clinical picture, the most often used are the **West-Haven criteria**. It is worth mentioning that the West Haven scale has been revised and updated to also include minimal hepatic encephalopathy before grade I HE [2-5].

Depending on the evolution in time, we can talk about:

- Episodic HE (if there is an interval greater than 6 months between episodes);
- Recurrent HE (if the interval between episodes is less than 6 months);
- Persistent HE (if neuro-psychiatric alterations, most often in the range of grades I-II, are permanently present, over which episodic aggravations in the range of grades III-IV may occur) [3,5].

Depending on the existence of precipitating factors, we can talk about:

- Spontaneous HE (when no potential triggering factors have been identified);
- Precipitated HE (when at least one factor is identified, that contributed to the decompensation of liver function and the onset of encephalopathy) [3,4].

1.2. EPIDEMIOLOGY

Hepatic encephalopathy affects approximately 40% of patients with cirrhosis [6]. Things get more complicated when it comes to minimal hepatic encephalopathy (MHE), since there is currently no clear diagnostic protocol. Dhiman et al have stated that the prevalence of MHE is between 30 and 84% (being higher in patients with more advanced liver disease), and have mentioned that MHE is associated with a lower health-related quality of life and with a less favorable general prognosis. The authors' recommendation was that all patients with liver cirrhosis should be evaluated for the presence of MHE, admitting at the same time that its diagnosis has not yet been standardized [7].

1.3. CLINICAL PICTURE

Hepatic encephalopathy can manifest through a wide spectrum of neurologic and psychiatric symptoms (largely reversible). Symptom severity can vary, from minor alterations of the sleep-wake cycle, to confusion, mental slowness, temporal-spatial disorientation and personality changes, with subsequent progression to somnolence, stupor and finally coma [8-10]. Sleep disturbances have been reported with a significantly higher prevalence in cirrhotic patients (and especially in those with MHE) than in the general population. The most often encountered are insomnias, excessive daytime somnolence and inversion of the sleep-wake rhythm, and their presence has been associated with decreased health-related quality of life [11,12]. The low quality of sleep in liver transplanted patients has been associated with a high level of anxiety and stress, as well as with the presence of MHE [13-15].

1.4. PARACLINICAL EVALUATION

1.4.1. SERUM AMMONIA AND OTHER BIOMARKERS

It is known that ammonia plays a central role in the pathogenesis of HE, which is why many clinicians choose to determine its serum level (for the diagnosis, assessment of severity and monitoring of HE) [16]. Determination of serum ammonia is not currently recommended by the American Association for the Study of Liver Diseases for the diagnosis or exclusion of

HE [4]. Although not as well studied as serum ammonia, some inflammatory markers (particularly interleukin-6 and interleukin-18) seem to correlate with the presence of HE. 3-Nitrotyrozine was investigated as a potential biological parameter in the early detection of MHE. The sensibility and specificity for MHE detection were 93% and 89%, respectively [17-19].

1.4.2. ELECTROENCEPHALOGRAM (EEG)

Patients with overt HE display a diffuse progressive slowing of cerebral electrical activity, initially associated with an increase, and afterwards with a decrease of the wave's amplitude, as well as with the appearance of triphasic waves [8,20,21]. According to the International Society of Hepatic Encephalopathy and Nitrogen Metabolism, EEG studies can be used to complement the neurological examination to: (1) confirm the presence of HE in patients with normal conscious states; (2) demonstrate the worsening or improvement of HE during follow-up; (3) exclude other causes of altered consciousness (such as non-convulsive status epilepticus) [22].

1.4.3. BRAIN MAGNETIC RESONANCE IMAGING (MRI)

Brain magnetic resonance imaging is the imaging modality of choice in hepatic encephalopathy. The MRI examination classically reveals T1 high-signal intensity changes with bilateral symmetrical distribution at the level of the globus pallidus, and occasionally involving the caudate nucleus or subthalamic nucleus [8,23]. Sometimes these can extend to the mesencephalon [24,25]. It is presumed that these changes are due to manganese depositions.

The frequency of these cerebral T1 hyperintensities is high. However, things aren't fully established concerning their clinical significance. Some authors (Pujol et al) have established a positive correlation between the signal intensity at the level of the globus pallidus on one hand, and the severity of liver cirrhosis (appreciated using the Child-Pugh score) and a positive history of HE on the other hand [26]. However, Thuluvath et al have stated that these imaging changes cannot be considered indicators of HE, since they correlated neither with the psychometric tests, nor with clinical encephalopathy or ammonia levels [27]. It remains to be determined what is the exact significance of the T1 high-signal changes at the level of the globus pallidus. It is worth remembering that these changes can diminish after liver transplantation [28].

1.5. NEUROPSYCHOLOGICAL ASSESSMENT

Neuro-psychological (or psychometric) tests play an important role in diagnosing MHE, since these patients display cognitive deficits that are subtle and difficult to evaluate on a routine examination. Of the neuro-psychological tests that are currently used in clinical practice, only the Psychometric Hepatic Encephalopathy Score and the Repeatable Battery for the Assessment of Neuropsychological Status have been recommended for the detection of MHE [29].

The main disadvantages of these tests are the high time required for administration, as well as the influence of the patients' educational level on performance.

EncephalApp Stroop Test

Over the last decade, with the widespread use of tablets and smartphones, a new psychometric test based on the Stroop effect was developed, named EncephalApp Stroop Test, which can be used in the form of an app on these devices (in a simple and fast manner).

This application was validated by Bajaj et al in two consecutive papers published in 2013 and 2015, respectively. The first paper was aimed at screening for MHE using EncephalApp Stroop Test and comparing the app to the standard psychometric tests. EncephalApp Stroop Test performances were weaker in patients with a history of overt HE or in patients with MHE diagnosed through psychometric testing. Also, there was a positive correlation between test results and severity of cirrhosis (appreciated using the MELD score) [30]. In the second paper, test-retest reliability and external validity were demonstrated, and a cut-off value of > 190 seconds was established for the detection of MHE [31].

1.6. PROGNOSIS

The presence of MHE is associated with decreased quality of life and is a risk factor for the onset of overt HE and for mortality. Because of diminished psychomotor performances, MHE constitues a major cause of premature retiring for cirrhotic patients, and interferes with the capacity to drive vehicles, leading to an increased risk of road accidents [32-34].

2. NEUROLOGICAL COMPLICATIONS OF LIVER CIRRHOSIS AND LIVER TRANSPLANTATION

2.1. ACQUIRED HEPATO-CEREBRAL DEGENERATION (AHD)

AHD is a rare neurological syndrome, with progressive worsening, and largely irreversible (thus distinguishing itself from episodic HE) [35]. AHD has been described in patients with chronic liver disease and portosystemic shunt (either spontaneous, or surgically placed). The prevalence of AHD in cirrhotic patients is between 0.8 – 2%, and men seem to be more frequently affected [36,37]. There is no clear association between AHD and the duration/severity of liver involvement. A central role in its pathogenesis seems to be played by manganese accumulation at the level of the globus pallidus. Another risk factor for the development of AHD is represented by recurrent episodes of hepatic coma or HE [38,39].

The clinical picture of AHD consists of a chronic neurological syndrome with an insidious onset and progressive worsening, which includes [35,40,41]: extrapyramidal signs (parkinsonism, tremor, choreoathetosis, dystonia, myoclonus and/or asterixis); ataxia; neuro-psychiatric involvement and/or cognitive decline. MRI shows T1 high-signal intensities at the level of the globus pallidus bilaterally. It is assumed that these anomalies represent local depositions of manganese [35,36,40,42]. Their mere presence in a cirrhotic patient is not however sufficient to establish the diagnosis of AHD, in the absence of clinical manifestations.

There is no specific treatment for AHD. It is worth mentioning that some cases of AHD were cured following liver transplantation [43,44]. In other patients however, liver transplantation did not improve the clinical picture (possibly due to the persistence of the portosystemic shunt) [36].

2.2. HEPATIC MYELOPATHY

Hepatic myelopathy is another rare complication, encountered in patients with chronic decompensated liver disease or with a co-existing portosystemic shunt [45]. The condition manifests as a progressive spastic paraparesis (or, more rarely, tetraparesis), without sensory

deficits or sphincter dysfunction [46,47]. The diagnosis of hepatic myelopathy is currently an exclusion diagnosis. Hepatic myelopathy can improve (at least partially) after liver transplantation [48].

2.3. POLYCYSTIC LIVER DISEASE (PLD)

Polycystic liver disease (PLD) is a rare genetic disease, with autosomal-dominant inheritance, in which the normal hepatic parenchyma is replaced by numerous cysts. The cause is represented by mutations of the genes that code for proteins implicated in fluid transport and in the growth of hepatic epithelial cells [49]. Most of the cases (80-80%) are associated with polycystic kidney disease (either autosomal-dominant, or autosomal-recessive) [50].

The prevalence of isolated PLD varies in the literature, but is significantly lower than that of autosomal-dominant polycystic kidney disease (under 0.01% versus 0.2%) [51]. On the other hand, polycystic liver disease is one of the main extrarenal manifestations of autosomal-dominant polycystic kidney disease (AD-PKD), and the prevalence of PLD in patients with AD-PKD is age-dependent, rising from 20% in the third decade, to 70% in the seventh decade [52].

The prevalence of cerebral aneurysms in patients with AD-PKD is higher than in the general population [53-55]. Given that the prevalence of cerebral aneurysms increases with age (both in the general population and in patients with AD-PKD), prospective studies are needed to evaluate the real prevalence of aneurysms in patients with isolated PLD.

2.4. NEUROLOGICAL COMPLICATIONS ASSOCIATED WITH LIVER TRANSPLANTATION

Neurological complications associated with liver transplantation occur in approximately 15 – 30% of receiving patients, usually within the first month after the transplant [56,57].

The risk of developing neurological complications is higher in patients transplanted with liver from a brain-dead donor than in patients transplanted with liver from a living donor. This is probably due to the shorter cold-ischemia time, as well as the better quality of the graft in the

case of living donors [58]. A series of factors are associated with the post-operative development of neurological complications: renal failure, hepato-renal syndrome, pre- and intra-operative dialysis, pre-operative encephalopathy, pre-operative mechanical ventilation and infections [59].

Also, neurological complications have been reported more often in patients transplanted for alcoholic liver cirrhosis or primary biliary cholangitis [60].

Of course, the use of chronic immunosuppressive treatment predisposes to opportunistic infections (including of the central nervous system), and immunosuppressants can also have direct neurotoxic effects [56]. The frequency of neurological complications seems to be similar between patients treated with tacrolimus and those treated with cyclosporine [58].

A classification of the main neurological manifestations (and their causes) is presented in the following [56, 61-66]:

1. *Post-transplant encephalopathy*
2. *Seizures*
3. *Opportunistic infections of the central nervous system*
4. *Osmotic demyelination syndrome*
5. *Headache*
6. *Immunosuppressant toxicity (calcineurin inhibitors)*
7. *Ischemic and hemorrhagic cerebrovascular events*
8. *Critical illness neuropathy and myopathy*
9. *Post-transplant neuro-cognitive deficits*

Currently, in Romania, all patients that are to be included on the liver transplantation waiting list undergo a standard neurological examination, as well as an EEG assessment. However, it is possible that this current protocol does not fully cover the needs of the cirrhotic patients, from a neurological point of view.

I hope that through the directions addressed in this paper to improve the role of the neurologist in the pre- and post-liver transplant assessment.

II. ORIGINAL PART

3. WORKING HYPOTHESIS AND RESEARCH OBJECTIVES

3.1. Diagnosis of minimal hepatic encephalopathy

Through this paper, we first of all aimed to implement a method for diagnosing minimal hepatic encephalopathy in the clinical practice. We chose to use and study the application EncephalApp Stroop test for this purpose. We were interested in whether the patients' performances were influenced by the severity of liver disease or by other clinical, demographic and biological factors.

3.2. Excessive daytime somnolence in cirrhotic patients

Another approach was represented by the assessment of excessive daytime somnolence, given its high prevalence in cirrhotic patients. We researched whether there is an association with the severity of liver disease, or with minimal hepatic encephalopathy (diagnosed through the EncephalApp Stroop test). To achieve this objective, we used a Romanian-translanted version of the Epworth sleepiness scale (ESS).

3.3. Neurological manifestations in pre- and post-liver transplant patients – neuro-gastroenterological correlations

Furthermore, we conducted a prospective study in which cirrhotic patients were monitored for the detection of any potential neurological complications, and for correlating these complications with the severity of liver disease, or with other relevant parameters. Patients who were liver transplanted over the course of the study were monitored for the detection of neurological complications secondary to liver transplantation and immunosuppressive therapy.

3.4. The risk of cerebral aneurysms in patients with polycystic liver disease

Last but not least, we aimed to evaluate the prevalence of saccular cerebral aneurysms in patients with polycystic liver disease, since this has been less studied regarding the association with cerebral aneurysms.

4. GENERAL RESEARCH METHODOLOGY

The studies which are presented in this paper took place between 2016-2024 at the Gastroenterology and Hepatology Department of Fundeni Clinical Institute, in Bucharest.

The studies conducted were prospective and observational. Each study also holds a descriptive component regarding the studied population.

All patients expressed beforehand an informed consent for participating in these studies. Confidentiality and personal data protection for each patient were respected. The studies received approval from the Ethics Comitee. Only patients which respected the inclusion and exclusion criteria for each study were included. We mention that during the COVID-19 pandemic, all measures regarding social distancing and sanitation were respected to prevent the spread of the coronavirus.

All patients underwent a standard neurological examination and an EEG asssessment prior to inclusion on the liver transplantation waiting list. MRI examinations were performed on a 1.5 Tesla MRI machine, and included the following sequences: T1, T2, T1SE, FLAIR, SWI, DWI, ADC, 2D-TOF, 3D-TOF and MR-Spectroscopy.

Patients' medical data were obtained through history, or through checking the observation sheet and/or consulting the treating physician. Imaging and laboratory results, as well as discharge papers were accessed using the hospital's information system (Hipocrate).

The process of data collection and processing was done with Microsoft Office Professional Plus 2021. Patients' personal data were introduced in a secured digital database. For statistical analysis, the program MedCalc Statistical Software version 20.221 was used.

The statistical results were presented in the form of graphs. This work was written using Microsoft Office Word. The partial results of the studies were presented in the form of articles in scientific papers indexed in international databases and in ISI. Some results were also presented in the form of posters at national and international congresses.

5. VALIDATION OF ENCEPHALAPP STROOP TEST FOR DIAGNOSING MINIMAL HEPATIC ENCEPHALOPATHY

5.1. SPECIFIC OBJECTIVES

First of all, we aimed to evaluate the prevalence of MHE among cirrhotic patients using the EncephalApp Stroop test application.

Also, we are interested in whether patients' performances correlate with the severity of liver disease, duration of disease, etiology of cirrhosis, history of overt HE, ammonia serum levels, as well as with other relevant biological and imaging parameters.

Last but not least, we want to establish if patients' performances are influenced by other factors, such as age, sex, educational level or the area of origin (urban/rural).

5.2. MATERIAL AND METHODS

We performed a cross-sectional observational study, in which 100 patients diagnosed with liver cirrhosis were evaluated for the presence of MHE using EncephalApp Stroop test.

Only patients who respected the inclusion and exclusion criteria, and who signed beforehand the informed consent were enrolled. Patients with neuro-psychiatric comorbidities, those diagnosed with Wilson disease, or patients with preexisting cognitive decline (as defined by an MMSE < 25 points) were excluded. The use of psychoactive medications (which could influence concentration or the reaction speed of the patient) represented another exclusion criterion. Moreover, patients with color blindness, uncorrected refractive errors, or those who cannot read, were also excluded, since testing could not have been optimally performed in these patients.

Testing took place on an Apple iPad Mini 4 tablet, using a Romanian-transplated version of the EncephalApp Stroop test. Each patient was evaluated during the day (in the morning), in a naturally-lit, airy, and noise-free room, with the patient seated at a table.

Liver disease severity was measured using the MELD and Child-Pugh scores. Data was collected regarding the educational level of the patients, area of origin, duration of cirrhosis, and presence of prior HE episodes.

In parallel, 45 adult subjects without liver disease were recruited, who respected the same exclusion criteria and also signed the informed consent regarding participation. Preparation and testing of the control-group were done under the same conditions as with the cirrhosis patients.

5.3. RESULTS

Mean age of the patients was 50 ±9 years-old (range: 28-62 years-old). 70% were males. 73% of patients were living in urban areas, and 50% were college graduates. In the case of the control-group, mean age was 51 ±13 years-old (range: 22-73 years-old). In the control group 76% of the participants were females (n=34). 93% of the subjects from the control-group were living in urban area (n=42), and 82% were college graduates (n=36). The overall age of the control-group (median: 53 years-old, IQR: 41 – 62.25 years-old) was similar to that of the patients' group (median: 52 years-old, IQR: 45.5 – 57 years-old) (p=0.4).

The most common etiology was viral hepatitis, which was encountered in 67% of the patients. Alcoholic liver disease was described as the main etiology in 20% of the patients. Mean duration of cirrhosis was 5 ±5 years (range: 0 – 22 years). A positive history of overt HE was reported in 23% of the patients. Portal vein thrombosis was noted in 25% of the cases.

The mean MELD score was 16 ±6 points, while the Child-Pugh score had a mean value of 8 ±2 points. There was a strong correlation between the two scores ($R=0.79$, $p<0.0001$). We also mention that 24% of the patients were diagnosed with type II diabetes mellitus.

The mean Stroop score was calculated for both groups. The median result of the control-group was 140.0 seconds (IQR: 128.2 – 154.2 seconds), while the median result obtained by the patients was 166.0 seconds (IQR: 150.4 – 192.0 seconds) ($p<0.0001$). Based on the currently available cut-off value (of >190 seconds), MHE was diagnosed in 25% of the patients.

A significant correlation between patients' performances and age was observed ($R=0.45$, $p<0.0001$). A further age-based stratification highlighted a significant difference between the

results of patients ≤ 50 years-old and those of patients > 50 years-old (p=0.0001). The correlation with age was stronger in the control-group (R=0.75, p<0.0001) [67].

There were no significant differences in the results obtained between male and female participants, as well as between rural and urban-dwelling participants, in either of the two groups. EncephalApp Stroop test results were not influenced by the educational level of the participants [68].

Patients' performances correlated with the severity of liver disease, as assessed by the MELD (R=0.28, p=0.005) and Child-Pugh scores (R=0.2, p=0.04). Patients with alcoholic liver disease performed more poorly (median: 177.5 seconds, IQR: 159.1 – 208.4 seconds) compared to the other etiologies (median: 162.1 seconds, IQR: 146.3 – 181.7 seconds) (p=0.02). The performances obtained by the patients did not correlate with the duration of liver cirrhosis (R= -0.08, p=0.4). Also, no significant differences were noted between patients with a history of overt HE and patients without such a history (p=0.24).

EncephalApp Stroop test results did not correlate with serum ammonia levels (R= -0.1, p=0.5). There was however an inverse correlation between test results and the level of glycemia (R=0.25, p=0.01). Moreover, diabetic patients performed less well than non-diabetic patients (p=0.003).

Hyponatremia, anemia and the presence of a low cholesterol level were associated with worse results of the patients. There were no significant differences of the results between patients who subsequently died (median: 173.1 seconds, IQR: 157.0 – 199.2 seconds) and (non-transplanted) patients who survived at one year (median: 157.7 seconds, IQR: 146.3 – 172.2 seconds) (p=0.1). The mean score of the patients who developed post-transplant neurological complications was 183.1 ±25.5 seconds, while the mean score of the patients who did not develop post-transplant neurological complications was 172.0 ±33.4 seconds. The difference was not statistically significant (p=0.3), however there was a trend for the Stroop scores to be higher among patients who developed post-transplant neurological complications.

6. INVESTIGATION OF EXCESSIVE DAYTIME SLEEPINESS AS A POSSIBLE MANIFESTATION OF MINIMAL HEPATIC ENCEPHALOPATHY

6.1. SPECIFIC OBJECTIVES

We aimed to evaluate the prevalence of excessive daytime somnolence in cirrhotic patients, and to correlate it with the degree of hepatic involvement, and with other clinical-biological and demographic parameters, respectively.

We wish to establish if the scores obtained by the patients correlate with their performances on the EncephalApp Stroop test. Lastly, we want to see if the patients' performances were associated with an increased risk of HE development during the follow-up period of one year.

6.2. MATERIAL AND METHODS

We performed a prospective observational study, in which we recruited 40 adult patients diagnosed with liver cirrhosis, which were included on the liver transplantation waiting list.

Only patients who respected the inclusion and exclusion criteria were enrolled. Excluded patients were: cirrhotic patients with overt HE; patients diagnosed with sleep pathologies (such as narcolepsy, sleep apnea syndrome, or restless legs syndrome); patients receiving medications with sedating effects; as well as patients with neuro-psychiatric comorbidities which could alter the sleep-wake cycle (for example: dementia or alcoholic withdrawal).

All patients were initially evaluated neurologically, and were asked if they have insomnias or daytime sleepiness episodes. Subsequently, patients received a questionnaire for the assessment of daytime sleepiness. We chose to use a Romanian-translated version of the Epworth sleepiness scale (ESS) (version 22 Jan 2018). The procurement and use of the version were carried out with the permission of the MAPI Research Trust. Scoring was done according to the current protocol, a score of ≥ 11 points being suggestive of excessive daytime somnolence.

Patients were subsequently monitored throughout a year for the onset of episodic HE and for assessing the risk of mortality.

6.3. RESULTS

Mean age of the patients was 53 ±12 years-old (range: 30-70 years-old). 60% of the patients were males (n=24). A viral etiology was encountered in 57.5% of the patients (n=23), hepatitis B±D virus being present in 37.5% of the patients (n=15), and hepatitis C virus being present in 20% (n=8). 22.5% of the patients complained of insomnias (n=9), whereas 20% complained of recurrent episodes of daytime somnolence (n=8). The ESS mean value was 5 ±4 points (95% CI: 4–7 points, $p<0.0001$) (range: 0-19 points; median: 4.5 points).

Patients with insomnias obtained a median score of 7 (IQR: 3.75 – 10 points), while patients without insomnias obtained a median score of 4 (IQR: 1.25 – 7 points), however the difference did not reach statistical significance (p=0.06). Patients who complained of daytime somnolence obtained a median score of 10 points (IQR: 7.5 – 11 points), which was significantly higher than the median score of 3.5 points (IQR: 1.5 – 6.5 points) obtained by the patients who did not have daytime somnolence (p=0.002) [69].

The results obtained at the ESS did not correlate with either the Child-Pugh score (R=0.15, p=0.4), or the MELD score (R=0.13, p=0.4). There was however an inverse correlation between ESS results and the serum level of fibrinogen (R= -0.32, p=0.04). Cirrhosis of HBV±HDV etiology was associated with higher scores (median: 6 points, IQR: 4 – 10.75 points) than the other etiologies (median: 3 points, IQR: 1 – 7 points) (p=0.02). ESS results were compared with those obtained by the patients on the EncephalApp Stroop test, and although there was a positive correlation between the two, it did not reach statistical significance (R=0.35, p=0.06).

Patients with a history of HE obtained a higher ESS score (median: 6 points, IQR: 4 – 9 points) than the other patients (median: 2.5 points, IQR: 1 – 6.5 points) (p=0.046). Patients were monitored for a year. 12.5% of them developed overt HE during follow-up (n=5). The median score of the patients who subsequently developed HE was 6 points (IQR: 4.25 – 12 points), while the median score of the other patients was 4 points (IQR: 2 – 7.75 points), however the difference was not statistically significant (p=0.2).

7. PRE- AND POST-TRANSPLANT EVOLUTION OF PATIENTS WITH LIVER CIRRHOSIS – NEURO-GASTROENTEROLOGICAL CORRELATIONS

7.1. SPECIFIC OBJECTIVES

We aimed to monitor the occurrence of neurological complications in patients with liver cirrhosis included on the liver transplantation waiting list, focusing on their frequency, clinical picture, prognosis, and association with the severity and type of liver cirrhosis, respectively. A particular topic was represented by the characteristic changes described in these patients on brain MRI, and their correlation with the liver disease.

Patients who were liver transplanted were followed-up for the occurrence of post-transplant neurological complications.

7.2. MATERIAL AND METHODS

We performed a prospective observational study, which took place over an 8-years period (2016-2024), and in which 196 adult patients awaiting liver transplantation were enrolled.

Only patients who signed the informed consent beforehand were included. Patient selection was based on inclusion and exclusion criteria. Patients diagnosed with Wilson disease were excluded, since this represents a separate clinical entity, with its own neurologic involvement. Patients admitted only for day hospitalization could not be properly investigated paraclinically, and were not included in the study.

The patients were periodically monitored biologically, endoscopically and through imaging. Prior to inclusion on the liver transplantation waiting list, all patients underwent a standard neurological examination and an electroencephalographic assessment (EEG). In the event of acute neurologic symptoms, the patients underwent brain imaging through computer tomography.

7.3. RESULTS

The mean age of the patients was 53 ±10 years-old (range: 25-74 years-old). Male persons represented 66% (n=130). 77% of the patients were living in urban areas (n=150). The most common etiology of cirrhosis was viral hepatitis, being encountered in 59% of the patients (n=115). Isolated alcoholic liver disease was present in 26% of the patients (n=51).

The mean duration of cirrhosis was 5 ±5 years (range: 0-22 years; median: 4 years). The prevalence of portal venous system thrombosis was 21% (n=42), while a positive history of overt HE was encountered in 32 % of the patients (n=63). Mean MELD score was 17 ±7 points (range: 7–40 points). Mean Child-Pugh score was 8 ±2 points (range: 5–13 points).

Mean venous ammonia level was 52 ±34 μmol/L (range: 2–163 μmol/L; median: 45 μmol/L). Serum ammonia correlated neither with the MELD score (R= -0.02, p=0.9), nor with the Child-Pugh score (R=0.03, p=0.8) [70].

Brain imaging in cirrhotic patients

36% of the patients (n=70) underwent brain imaging using MRI. The characteristic T1 high-signal intensity changes with symmetrical distribution at the level of the globus pallidus were encountered in 83% of the patients (n=58). In 21% of the cases (n=15), the T1 hyperintensity extended to the cerebral peduncles. One of the patients was diagnosed through imaging with a gigantic arachnoid cyst at the level of the left cerebral hemisphere, the presence of which did not constitute a contraindication for liver transplantation [71].

The presence of globus pallidus T1 hyperintensities was associated with a mean MELD score of 17 ±7 points, and with a median Child-Pugh score of 8 points (IQR: 7 – 10 points), while their absence was associated with a mean MELD score of 20 ±7 points, and with a median Child-Pugh score of 9 points (IQR: 7.25 – 10.5 points). The differences were not significant (p=0.2 for the MELD scores and p=0.8 for the Child-Pugh scores).

The median age of the patients with T1 high-signal brain changes was 51.5 years-old (IQR: 44 – 60 years-old), and that of the patients without imaging changes was 53.5 years-old (IQR: 47 – 60 years-old) (p=0.4). The median duration of liver disease in patients with T1 high-signal brain changes was 4 years (IQR: 1 – 7 years), and that of the patients without imaging changes was 3 years (IQR: 2 – 8 years) (p=0.9).

Males were more likely to exhibit brain T1 high-signal changes than females: X^2 (1, N=70) = 6.2, p=.01.

It is worth mentioning that the level of serum hemoglobin was lower in patients without brain imaging changes (9.8 ±2.2 g/dL), compared to the patients in which the hyperintensities were present (11.4 ±2.1 g/dL) (p=0.04). The median value of serum ammonia was 57 μmol/L (IQR: 25.25 – 81 μmol/L) in patients with cerebral T1 changes, and 32 μmol/L (IQR: 21.5 – 58.5 μmol/L) in patients without imaging changes. The difference was not however statistically significant (p=0.2).

Varying degrees of brain atrophy were described in 44% of the patients (n=31). Patients in whom brain atrophy was described were older (56 ±8 years-old) than the other patients (47 ±10 years-old) (p=0.0002). Patients with atrophic changes presented more episodes of HE in the past (median: 1 episode, IQR: 0 – 2 episodes) as compared to the other patients (median: 0 episodes, IQR: 0 – 1 episode) (p=0.0005). The Child-Pugh score was higher in patients with brain atrophy (median: 9 points, IQR: 8 – 11 points) than in the other patients (median: 8 points, IQR: 7 – 9 points) (p=0.03).

7.3.1. Acquired hepato-cerebral degeneration

Based on the clinical picture, acquired hepato-cerebral degeneration (AHD) was suspected in 3.5% of the patients (n=7), all of whom were males. The main etiologies were viral hepatitis with HBV+HDV in 3 cases, alcoholic liver disease in 2 cases and HCV infection in the other 2 cases. The median age of the patients with AHD was 62 years-old (IQR: 56.5 – 63.75 years-old). By comparison, the median age of the other male cirrhotic patients was 53 years-old (IQR: 46.25 – 60 years-old), the difference being statistically significant (p=0.03). The median duration of cirrhosis among patients with AHD was 7.5 years (IQR: 3 – 12 years), while that of the other male patients was 4 years (IQR: 1 – 7 years), however the difference did not reach statistical significance (p=0.09). All patients with AHD presented clinically with an akinetic-rigid parkinsonian syndrome, with insidious onset and slow-progressive evolution. In 3 cases ataxic paraparesis was also associated [72].

A positive history of HE was reported in all patients with AHD, as compared to only 31% in the other male patients (n=38), X^2 (1, N=130) = 13.9, p=.0002.

The MELD score of the patients diagnosed with AHD (median: 22 points, IQR: 15.25 – 24.75 points) did not differ significantly from the MELD score of the other male patients (median: 18 points, IQR: 13 – 22 points) (p=0.2). All patients with AHD presented T1 hyperintensities involving the globus pallidus, however these imaging changes were also described in the absence of the clinical diagnosis of AHD, such that no clear association could be established between the two: X^2 (1, N=70) = 1.6, p=.2.

7.3.2. Cerebral hemorrhages

During the follow-up period, cerebral hemorrhages were encountered in 2.5% of the patients (n=5). These were associated with a high mortality rate (80%). The mean age of the patients at the time of brain hemorrhage occurrence was 53 ±14 years-old (range: 36-66 years-old) (median: 61 years-old, IQR: 51 – 63.75 years-old). The INR value was significantly higher in patients with cerebral hemorrhage (median: 2.55, IQR: 1.9 – 3.7) when compared to the other patients (median: 1.5, IQR: 1.3 – 1.7) (p=0.02). The MELD score of the patients with cerebral hemorrhage had a median value of 31 points (IQR: 22.5 – 35.25 points), while the MELD score of all the other patients had a median value of 16 points (IQR: 11 – 22 points) (p=0.008). The Child-Pugh score was also higher in patients with cerebral hemorrhage (median: 12 points, IQR: 10 – 13 points) as compared to the other patients (median: 8 points, IQR: 7 – 10 points) (p=0.01).

7.3.3. Neurological complications of liver transplantation

Out of all the patients, 34% have been liver transplanted during the follow-up period (n=66). The mean age at the time of liver transplant was 51 ±11 years-old (interval: 30-70 years-old). 70% of the patients were males (n=46).

Most transplant interventions were performed with liver from brain-dead donors (95%). In 8% of the cases, the liver was perfused and oxygenated beforehand with the liver assist device. In 5% of the cases, the transplant was performed with right-sided half-liver from a live donor. The survival rate of the transplanted patients was 77%. The mortality rate was 14% (n=9), and most of the deaths (11%) occurred in the first year after the transplant (n=7).

The one-year survival rate was thus calculated at 89% (being similar with that reported by other countries). The five-year survival rate was 70% (n=21), with the mention that only 30

patients could be included in the analysis. The others were either lost during follow-up, or had not yet reached 5 years since the liver transplantation.

The prevalence of early neurological complications was 27% (n=18). Of these, the most common was post-transplant encephalopathy, which affected 18% of the patients (n=12). In 8% of the cases (n=5) epileptic seizures were reported. Other reported neurological complications included: tremor (2 cases), headache (one case), dysarthria (one case), sleep disturbances (one case) and pontine myelinolysis (one case).

There were no age-related differences between transplanted patients who developed neurological complications and the other transplanted patients (p=0.1). The risk of neurological complications was similar between males and females: X^2 (1, N=63) = 0.03, p=.8.

Also, the occurrence of neurological complications was not influenced by the severity of liver disease. Transplanted patients who developed neurological complications had a median MELD score of 18.5 points (IQR: 11 – 21 points), while patients without neurological complications had a median MELD score of 16 points (IQR: 11 – 21.25 points) (p=0.8).

The median duration of liver cirrhosis was 5 years (IQR: 2.75 – 7 years) in patients with neurological complications, and 3 years (IQR: 1 – 6 years) in the other patients, the difference not being statistically significant (p=0.09). Moreover, the presence of HE episodes in the past did not predispose to the occurrence of neurological complications: X^2 (1, N=47) = 0.99, p=.3. The presence of alcoholic liver cirrhosis was not a predispozing factor for the development of early post-transplant neurological complications: X^2 (1, N=59) = 0.84, p=.35.

The risk of neurological complications was higher in patients transplanted with liver perfused by the liver assist device than in the other patients transplanted with liver from brain-dead donors: X^2 (1, N=57) = 9.9, p=.0016. The risk of neurological complications was also higher in patients transplanted with liver from living donors than in patients transplanted with liver from brain-dead donors: X^2 (1, N=59) = 4.3, p=.038. The development of neurological complications was associated with a higher mortality risk: X^2 (1, N=59) = 4.05, p=.044.

The presence of T1 hyperintensities involving the globus pallidus was not associated with an increased risk of post-transplant neurological complications: X^2 (1, N=20) = 1.4, p=.2.

8. ESTABLISHING THE PREVALENCE OF CEREBRAL ANEURYSMS IN PATIENTS WITH POLYCYSTIC LIVER DISEASE

8.1. SPECIFIC OBJECTIVES

We aimed to assess the prevalence of cerebral aneurysms in patients with isolated polycystic liver disease (PLD), who were included on the liver transplantation waiting list. Also, we aimed to assess the risk of rupture of the aneurysms, by dynamically monitoring the patients.

A secondary objective was to establish a possible correlation between the severity of polycystic disease and the degree of hepatic and neurologic involvement. Patients who were diagnosed with PLD associated with autosomal-dominant polycystic kidney disease (AD-PKD) were also included in the study, the aim being to compare the two groups of patients.

8.2. MATERIAL AND METHODS

We performed a prospective observational study, which took place during a 6-years period (between 2017-2022). We followed-up patients with polycystic liver disease (isolated or associated with AD-PKD), both from a clinical point of view, and especially from an imaging point of view, in order to detect potential cerebral aneurysms and cerebrovascular events.

Brain imaging assessment was done on a 1.5 Tesla MRI machine. The degree of hepatic dysfunction was appreciated using the MELD score, while the renal dysfunction (if present) was evaluated through the serum creatinine level and by calculating the creatinine clearance (Cockcroft-Gault formula).

8.3. RESULTS

In total, 18 patients were enrolled, with a mean age of 52 ±5 years-old (range: 45-60 years-old). The mean age at the time of PLD diagnosis was 37 ±12 years-old. There was a clear predominance of female patients (n=16). Mixed forms of the disease with hepato-renal involvement (PLD associated with AD-PKD) were encountered in 9 cases, whereas isolated PLD was encountered in the other 9 cases. There were no significant differences between the

age of the patients with isolated PLD (52 ±5 years-old) and that of the patients with hepato-renal involvement (51 ±4 years-old) (p=0.7). Gender distribution was also identical between the two groups.

A positive family history was encountered in 39% of the cases (n=7), the majority of which were reported in patients with isolated PLD (n=5).

The presence of a post-transplant status was noted in 3 patients (all of which had mixed hepato-renal involvement): the first patient received a kidney transplant (in 2013), the second received a liver transplant (in 2013), and the third received both a kidney transplant (in 2004), and a liver transplant (in 2014).

The mean MELD score was 8 ±2 points (range: 6-12 points). There were no differences between the MELD scores of the patients with isolated PLD (8 ±2 points) and the MELD scores of the patients with mixed hepato-renal involvement (9 ±2 points) (p=0.3).

Cerebral aneurysms were described in only one female patient (diagnosed with AD-PKD), which corresponded to a total prevalence of 5.55%. This patient presented three aneurysms:

- Fusiform, with a diameter of 5.5 mm, extending over a length of 7 mm at the level of the right-sided vertebral artery, not thrombosed;
- Saccular, with a diameter of 9.7 mm, involving the M1 segment of the right-sided middle cerebral artery, not thrombosed;
- Saccular, with a diameter of 3.0 mm, involving the M1 segment of the left-sided middle cerebral artery, not thrombosed.

None of the patients with isolated polycystic liver disease were found to have cerebral aneurysms [73].

No cerebrovascular events or subarachnoid hemorrhages were recorded during the follow-up period. Instead, one of the female patients (with polycystic hepato-renal disease) was liver transplanted, without any remarkable peri- or post-operative events.

9. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

9.1. Diagnosis of minimal hepatic encephalopathy

EncephalApp Stroop test proved to be a fast and intuitive method for diagnosing MHE.

The patients' performances were primarily influenced by age. For this reason, we consider that a single cut-off value for the diagnosis of MHE is not sufficient, and age-dependent cut-off values should be implemented. In our study, there was a statistically significant difference between the results of patients aged ≤ 50 years-old and patients aged > 50 years-old, so implementing a cut-off value for each of these age groups would be justified.

The educational level and the area of origin of the participants (urban versus rural) did not influence the performances, which constitutes an advantage of this application over other types of psychometric evaluations. Patients' performance was also influenced by the severity of liver disease, as well as by the presence of other comorbidities, such hyperglycemia/diabetes mellitus, chronic alcoholism, anemia, hyponatremia and low levels of serum cholesterol.

In view of all of the above, we consider EncephalApp Stroop test to be an efficient method, which should be implemented in clinical practice for the quick detection of MHE.

9.2. Excessive daytime somnolence in cirrhotic patients

The Epworth sleepiness scale represents a quick and easy method to apply in clinical practice, for identifying excessive daytime somnolence in cirrhotic subjects. Patients' scores did not correlate with the severity of liver disease in our study. But there was a negative correlation with the serum level of fibrinogen. Patients with HBV±HDV infection obtained higher scores compared to the other etiologies.

Patients with a history of overt HE obtained higher scores than patients with no history of HE. However, the presence of a higher score did not have any prognostic value for the subsequent occurrence of overt HE. There was a correlation (albeit not statistically significant) between the ESS scores and the EncephalApp Stroop test results. The exact impact of daytime somnolence on the patients' cognitive performances remains to be established.

9.3. Neurological manifestations in pre- and post-liver transplantation – neuro-gastroenterological correlations

T1 hyperintensities involving the globus pallidus were described in 83% of the patients, however their presence was not associated with the severity of liver disease.

Development of acquired hepato-cerebral degeneration correlated with age, male sex, and a prior history of HE, but not with the severity and duration of liver disease.

Occurrence of cerebral hemorrhages in cirrhotic patients was associated with a high mortality rate (80%). Patients who developed cerebral hemorrhage had higher Child-Pugh and MELD scores, and the median value of the INR was also higher.

Early neurological complications were encountered in 27% of the patients, and their occurrence was associated with a high risk of mortality. Severity of liver disease, duration of cirrhosis, and a positive history of HE did not predispose to the development of neurological complications. The most common early neurological complication was post-transplant encephalopathy.

Surprisingly, transplantation with liver from living donors was more often associated with neurological complications in our study, which does not coincide with the literature. However, the sample size of these patients was small, such that these results will have to be confirmed by a larger study.

9.4. The risk of cerebral aneurysms in patients with polycystic liver disease

In our study, no cerebral aneurysms were encountered in patients with isolated polycystic liver disease, but in only one female patient with autosomal-dominant polycystic kidney disease with liver involvement. However, the small size of the patient group constitues a limitation of this study. Considering the available data from the literature, as well as the results of this study, we cannot confirm with certainty if isolated polycystic liver disease is associated or not with an increased risk of cerebral aneurysms.

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