MELD BASED COMPARISON OF HOSPITALIZATIONS FROM HEPATIC ENCEPHALOPATHY IN PATIENTS WITH ADVANCED LIVER DISEASE ON RIFAXIMIN AND LACTULOSE COMBINATION THERAPY

HASSETT M, RAMIREDDY S, MANTRY PS, HEPATOLOGY 2011;54 (SUPPL S1):1263A-1264A, POSTER 1917, THE LIVER MEETING 2011

Purpose:

Rifaximin is a non-absorbable antibiotic which is approved for the treatment of Hepatic Encephalopathy (HE) in the United States. The experience using rifaximin in preventing hospitalizations from HE in patients with advanced liver disease (MELD ≥20) is limited. Our goal was to specifically address this issue with our center data.

Results:

220 patients with complete data were analyzed. The median age was 58; 63% of the cohort was male; 69% of the cohort was Caucasian. In terms of disease etiology, Chronic Hepatitis C, Laennec's cirrhosis, primary liver cancer and NASH accounted for majority of the cohort (36% 18% 15% and 14% respectively). During our observation period, a total of 638 hospitalizations at our center were recorded. Of these, 195 hospitalizations were due to HE, whereas 443 were due to other causes. We observed that patients with a MELD <20 had an average 2.5 hospitalizations per patient for HE (49 patients and 126 hospitalizations) and those with a MELD ≥20 had an average of 1.6 hospitalizations per patient for HE (43 patients and 69 hospitalizations). At the same time, patients who had a MELD score <20 had 3.29 hospitalizations per patient for HE unrelated causes (79 patients/260 hospitalizations) and those whose MELD was ≥20 had 3.73 hospitalizations per patient for causes not related to HE (49 patients/183 hospitalizations). The two groups were similar in terms of demographics and disease etiology.

Methods:

We examined a total of 254 consecutive patients who were on a combination of rifaximin and lactulose who had been evaluated for a liver transplant at our center. We divided the cohort into two groups- patients whose MELD was ≥20 and patients whose MELD was <20. Patients who received <3 months of rifaximin and lactulose and those with incomplete data were excluded.

Conclusion:

In our experience, HE related hospitalizations were lower in patients whose MELD ≥20 who were on combination with lactulose and rifaximin compared to patients with MELD < 20. In contrast, patients whose MELD ≥20 had greater incidence of hospitalizations from non HE causes which may be an expected result owing to the overall increased severity of their liver disease. We noted that the preventive effect of rifaximin and lactulose combination therapy was pronounced in patients whose MELD was ≥20. As there is increasing experience in this group of patients, it remains to be seen if this observation continues to hold amongst other patient cohorts or in future prospective clinical trials in patients with very advanced liver disease.

EMBOLIZATION OF SPONTANEOUS PORTOSYSTEMIC SHUNTS IN CIRRHOTIC PATIENTS WITH REFRACTORY HEPATIC ENCEPHALOPATHY: A SINGLE CENTER PROSPECTIVE EXPLORATORY STUDY.

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HEPATOLOGY 2011;54 (SUPPL S1):1244A POSTER 1876, THE LIVER MEETING 2011

Background:

Refractory hepatic encephalopathy (HE) remains a major cause of morbidity in cirrhotic patients. A frequent phenomenon in these patients are large spontaneous portosystemic shunts (SPSSs). We hypothesized that embolization of these SPSSs might lead to improved control of HE and subsequent quality of life and health-economic burden.

Methods:

Between June 2008 and June 2010, we selected patients with cirrhosis without decompensation but with refractory HE with SPSSs on abdominal MRI. Refractory HE was defined as recurrent episodes of HE (≥ grade 2 according to New Haven-classification) with at least 2 hospitalisations after start of standard therapy (n=8, 80%), which consisted of daily lactulose ± selective intestinal decontamination, or as persisting HE 30 days after start of standard therapy at first hospital admission (n=2, 20%) (maximal grade HE ≥ III in 90%). Both efficacy (assessed by grade of HE and number & duration of hospitalisations within 100 days pre- and post-treatment) and short- and long-term complications (procedural and portal hypertensive-related) were analyzed.

Results:

In total 14 patients were screened of which 10 were technically eligible for embolization (7 women/ 3 men, mean age 63, predominantly post-alcoholic cirrhosis, mean Child B8 - MELD 14). Considered culprit SPSSs were : recanalized paraumbilical veins (n=6), splenorenal shunts (n=3) and a shunt between the superior mesenteric and right ovarian vein (n=1). There were no procedure-related complications . All patients are still alive and none of them is transplanted. Since embolization, both the number of hospitalizations (2 episodes per 100 days pre-embolization vs. 0.15 episodes per 100 days post-embolization, P=0.01) and days-spent-in-hospital because of HE (47 days pre vs. 10 days per 100 days post-embolization, P=0.04) were significantly reduced. Sub-analysis of all patients with episodes of grade III-IV HE before embolization showed that 75% of them did not experience any episode of HE after embolization. The grade of ascites (assessed at 1 & 3 months) and of gastro-esophageal varices (assessed endoscopically after 3 months post-embolization) was comparable to before intervention. No episodes of variceal hemorrhage or renal function deterioration was observed.

Conclusion:

Selective embolization of SPSSs in a group of cirrhotic patients with low MELD (and therefore low priority for transplantation) with invalidating therapy-refractory recurrent or persistent HE, leads to a maintained and improved quality of life and health-economic balance. Moreover, this procedure did not aggravate the portal hypertensive syndrome.

MINIMAL HEPATIC ENCEPHALOPATHY: POSSIBILITIES OF DIETARY FIBERS TREATMENT

POSTER 154

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Aim:

To study effects of dietary fibers (psyllium husks, Mucofalk) in patients with chronic liver diseases (CLD) on the course of minimal hepatic encephalopathy (MHE).

Materials and methods:

45 patients with CLD and MHE were examined. In group 1 (25 patients) the treatment consisted of essential phospholipids (2 capsules t.i.d.) and Mucofalk (5 g of granules t.i.d.) for 4 weeks. Group 2 (20 patients) was treated with essential phospholipids (2 capsules t.i.d.) and lactulose (30 ml once a day in the morning) for 4 weeks. Clinical, biochemical and psychometric parameters (TLC, LT) and intestinal dysbiosis were controlled on day 1 and at 4 weeks. In all patients with CLD and MHE (100%) dysbiosis was found. Intestinal normal flora microorganisms (Bifidobacteria, Lactobacilli, E. coli with normal enzymatic activity) were found to be decreased while opportunistic pathogenic flora (Enterococci, Candida, hemolytic microorganisms) increased.

Results:

After the treatment patient's general well-being improved, asthenic and dyspeptic syndrome manifestations decreased in 17 patients (68.0%) from group 1 and in 14 patients (70.0%) from group 2. Repeated bacteriological feces analysis in 1 and 2 groups of patients showed the improved quantitative and qualitative parameters of intestinal microflora content (differences are significant, $p < 0.05$). Psychomotor parameters restoration due to TLC and LT were registered in 17 (68.0%) of patients from group 1 and in 14 (70.0%) patients from group 2. Significant inverse correlation relation between TLC and LT and the level of Lactobacilli ($r = -0.29$, $p < 0.05$, and $r = -0.20$, $p < 0.05$) and direct relation with Clostridia growth ($r = 0.20$, $p < 0.005$, and $r = -0.19$, $p < 0.05$), Staphylococcus aureus ($r = 0.24$, $p < 0.05$ and $r = 0.23$, $p < 0.05$), Candida ($r = 0.41$, $p < 0.05$ and $r = 0.36$, $p < 0.05$) and TLC time and hemolytic microorganism growth ($r = 0.24$, $p < 0.05$) were found in the study.

Conclusion:

Dietary fibers (psyllium, Mucofalk) positively influenced qualitative and quantitative intestinal microflora contents, promoted MHE resolution. The efficacy of MHE treatment with psyllium husks (Mucofalk) is comparable with efficacy of lactulose use.

METAL METABOLISM IMPAIRMENT IN PATIENTS WITH HEPATIC ENCEPHALOPATHY

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POSTER 582

Background and Aims:

Metal overload contributes to neuronal oxidative stress, which has been strongly implicated in the pathogenesis of hepatic encephalopathy (HE). Further than manganese, liver prevents other metal overload by producing scavenger proteins, like Ceruloplasmin (Cp) and Transferrin (Tf). Cp is required for copper metabolism and for the oxidation of toxic ferrous iron into ferric iron, therefore permitting its transport in plasma by Tf in an equilibrate antioxidant Cp/Tf system. We aimed to investigate if alterations in metal homeostasis could play a role in HE pathogenesis.

Methods:

Seventeen normal controls (CON), 8 patients with chronic hepatitis (CH), and 22 cirrhotics, further subdivided into 2 groups according to the absence (NENC, 11 patients) or presence (ENC, 11 patients) of history and/or on-going signs of overt HE, were enrolled. All patients and controls underwent: -determination of Cp, Cp activity, Tf, iron and total copper plasma concentrations, and of Tf saturation and Cp/Tf ratio; -cognitive evaluation with repeatable-battery-for-the-assessment-of-neuropsychological-status (RBANS); electroencephalography. A subgroup of patients was tested by specific MRI sequences in order to evaluate manganese and iron brain amount (Copper is paramagnetic).

Results:

In psychometry, cirrhotics performed worse with respect to CON and CH ($p < 0.01$), and ENC worse than NENC ($p < 0.05$). Specific EEG alterations were observed only in ENC, while other EEG alterations, compatible but not specific for HE, were observed in ENC and NENC ($p < 0.01$). Biochemical variables are reported in Table 1. Copper levels were significantly reduced in ENC, while iron concentrations did not show significant changes. While showing nonsignificant fluctuations in CH and NENC, Cp, Cp activity, Tf, Tf saturation and Cp/Tf ratio were significantly altered in ENC. MRI analysis showed iron and manganese basal ganglia overload in cirrhotic patients with respect to CON and CH ($p < 0.05$).

	CON	CH	NENC	ENC
Cp (mg/dl)	28 (23,5 - 32)	24 (22 - 28)**	28 (18 - 35)	23 (15 - 28,5)**
Cp activity (UI/L)	102 (76 - 135,5)	84,5 (52,6 - 111,5)*	111,6 (33,3 - 176,6)	46,2 (8,2 - 107)** ++ &&
Tf (g/L)	2,5 (1,7 - 3)	2,6 (2,1 - 3,1)	2,7 (1,4 - 4,8)	1,5 (0,58 - 4,4) ** ++ &&
Tf saturation %	27,5 (6 - 64,6)	25,1 (18,4 - 40,9)	29,5 (11,5 - 95)	67 (12,8 - 152)** +
Cp/Tf ratio (AU)	10,7 (9 - 14,6	8,8 (7 - 12,5)	9,7 (6 - 14,8)	16 (6 - 28)** ++ &&
Iron (ug/dl)	89 (18 - 148)	80 (61 - 147)	111 (61 - 301)	82 (65 - 192)
Total Copper (AU)	15,5 (6-21)	11,7 (8,2-17,2)	14,7 (7,3-19,5)	8 (6,2-11) ** ++ &&

*p<0,05 vs CON, **p<0,01 vs CON; +p<0,05 vs CH, ++p<0,01 vs CH; &p<0,05 vs NENC, &&p<0,01 vs NENC.[Table 1]

Conclusions:

Strong alterations in liver function could contribute, further to manganese, to iron brain accumulation, oxidative stress and development of HE. A reduced Cp activity justify low total copper levels in ENC, while free copper is possibly increased and deposited in tissues (similarly to Wilson disease).

SELECTED DOMAINS BUT NOT SUMMARY SCORE OF MINI-MENTAL STATE EXAMINATION CORRELATE WITH HEPATIC ENCEPHALOPATHY IN PATIENTS WITH LIVER CIRRHOSIS. A PROSPECTIVE, QUANTIFIED ELECTROENCEPHALOGRAPHY STUDY

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POSTER 598

Background and Aims:

Mini-mental state examination (MMSE) is commonly used by neurologists in the appraisal of cognitive mental status. An experience with MMSE in monitoring/evaluation of the severity of hepatic encephalopathy (HE) is very limited. We therefore investigated the significance of MMSE in the assessment of HE in patients with cirrhosis.

Methods:

Eighty nine patients: 59 males and 30 females, aged 55±12 years (range 18-87) underwent detailed neurological examination applying West Haven criteria, MMSE and closed-eye electroencephalography (EEG) all performed by one experienced neurologist. Spectral-EEGs was done on the transverse derivation P3-Pz/P4-Pz in the frequency range of 0,5-30Hz. Preselected 80-100s periods of artifact-free recording, split into 5s epochs were analyzed with Fast Fourier Transformation. Mean dominant frequency (MDF) was calculated and relative power of delta (0.5-4.0Hz), theta (4.0-8.0Hz), and alpha (8.0-13.0Hz) and beta (13.0-30.0Hz) rhythms were calculated. EEG results were then graded using the thresholds proposed by Amodio et al (J Hepatol2008;346-353).

Results:

Neurological examination identified 45 (51%) patients with overt HE: 23 (26%) in grade 1, 16 (18%) in grade 2 and 6 (7%) in grade 3 HE according to West-Haven criteria. MMSE (scores in most domains) were independent from age, gender and education. Only one domain (copy of pentagons) was related to patients` age ($p=0.02$). There were significant correlations between MMSE (total score and all domains) and severity of liver disease (Child-Pugh classification). MDF showed correlations with following domains: orientation to time ($p=0.05$) calculation ($p=0.04$), recall ($p=0.02$) and copy of pentagons ($p=0.05$). We observed significantly reduced MMSE scores in the following domains: orientation to time ($p=0.02$), orientation to place ($p=0.01$), calculation ($p=0.01$) and recall ($p=0.04$) in patients with more severe HE. MMSE summary score did not correlate with both MDF and severity of HE according to West-Haven criteria.

Conclusions:

While MMSE summary score has a limited specificity in terms of detecting HE, its several domains including orientation to time, orientation to place, calculation, recall and copy of pentagons may prove to be useful as a part of a more detailed assessment of HE.

PRIMARY PROPHYLAXIS OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS: AN OPEN LABELED RANDOMIZED CONTROLLED TRIAL OF LACTULOSE VERSUS NO LACTULOSE

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POSTER 601

Background and Aims:

Development of hepatic encephalopathy (HE) is associated with poor prognosis in patients with cirrhosis. Lactulose is used for the treatment of HE. There is no study on the prevention of HE using lactulose in patients who never had HE earlier.

Patients and methods:

Consecutive cirrhotic patients who never had an episode of HE were randomized to receive lactulose (Gp-L) or no lactulose (Gp-NL). All patients were assessed by psychometry [(number connection test (NCT-A and B), figure connection test if illiterate (FCT-A and B), digit symbol test (DST), serial dot test (SDT), line tracing test (LTT)] and critical flicker frequency test (CFF) at inclusion and after 3 months. These patients were followed monthly for development of overt HE.

Results:

Of 250 patients screened, 120(48%) meeting the inclusion criteria were randomized to Gp-L(n=60) and Gp-NL(n=60). Twenty one (20%) of 105 patients followed over a median follow up of 12 mo developed an episode of overt HE. Six (11%) of 55 in the lactulose (Gp-L) group and 15(30%) of 50 in the Gp-NL (p=0.02) developed HE. Ten (20%) of 50 patients in Gp-NL and 5(9%) of 55 patients in Gp-L group died, p=0.16. Number of patients with MHE were comparable in two groups at baseline (Gp-L vx Gp- NL, 32:36, p=0.29). Lactulose improved MHE in 66% of patients in Gp-L. Taking a cutoff < 38Hz sensitivity and specificity of CFF in predicting HE at baseline (52% and 77%) and at 3 month of treatment was (52% and 82%). On multivariate analysis CTP score and presence of MHE at baseline is significantly associated with development of HE.

Conclusion:

Lactulose is effective for primary prevention of hepatic encephalopathy in patients with cirrhosis.

METFORMIN PREVENTS OVERT HEPATIC ENCEPHALOPATHY (HE) IN CIRRHOTICS: A RETROSPECTIVE OBSERVATIONAL STUDY

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POSTER 606

Background and Aims:

To assess the impact on the development of hepatic encephalopathy (HE) of metformin use in a cohort of patients with well-characterized cirrhosis from minimal hepatic encephalopathy.

Methods:

One-hundred and ninety-eight cirrhotic patients were included with different etiologies: 46.5% alcoholic cirrhosis, 37.4% HCV-related and 16.2% others; 141 males and 57 females, with a mean age of 57±11 years. Child-Pugh: 6.2±1.5 and MELD: 10±4. Patients were classified as insulin sensitizers experienced (metformin with or without pioglitazone) (n=46); cirrhotics with type 2 diabetes mellitus treated with insulin (n=25); and non-diabetics or diabetics with dietetic treatment (n=126). Metformin was used during 35.5 ± 26.6 months. Baseline analysis, using commercial test, included: insulin, glucose, glucagon, leptin, adiponectin, IL-6, AST, ALT and HOMA-IR. TACC haplotype in glutaminase gene was obtained. MHE was measured by psychometric tests or critical flicker frequency. Oral glutamine challenge was altered if > 128mg/dL. Primary end-point was the hepatic encephalopathy. Secondary end-points were exitus and liver transplantation. We used the Kaplan Meier method to determine for univariate analysis and Cox regression for multivariate analysis.

Results:

Hepatic encephalopathy was developed in 24.7% (49/198): 31.8% (48/198) in untreated patients and 2.2% (1/46) in treated with metformin. In univariate analysis, the metformin use decreased HE (log Rank 13.35; p=0.000) and decreased Orthotopic liver transplant (log Rank 5.1; p=0.024) and improved survival (log Rank 4.3; p=0.038). In multivariate analysis by Cox regression, metformin use [H.R. 10.27 (95% CI: 1.4-75.24); p=0.022], diagnosis age [H.R. 1.05 (95% CI: 1.02-1.08); p=0.001], Child-Pugh [H.R. 1.30 (95% CI: 1.04-1.63); p=0.022] and MELD index [H.R. 1.13 (95% CI: 1.04-1.24); p=0.005] were independently associated with EH. We analyzed metformin use in a cohort of patients with Child-Pugh A stage (n=135), metformin [H.R. 9.3 (95% CI: 1.21-71.66); p=0.032], HOMA-IR [H.R. 1.14 (95% CI: 1.03-1.27); p=0.014], Child-Pugh [H.R. 0.25 (95% CI: 0.06-0.98); p=0.046] and MELD [H.R. 1.24 (95% CI: 1.04-1.49); p=0.017] were independently associated with EH development risk.

Conclusions:

Metformin use seems to be protective against hepatic encephalopathy in cirrhotic patients. After these results, it may be necessary to start a randomized double blind placebo-controlled clinical trial to confirm these findings.

PERSISTENCE OF COGNITIVE IMPAIRMENT AFTER OVERT HEPATIC ENCEPHALOPATHY: AN INTERNATIONAL, MULTI-CENTER PROSPECTIVE STUDY

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POSTER 611

Background:

There is growing evidence that cognitive dysfunction may persist after recovery from overt HE(OHE). This needs to be confirmed in multi-center studies.

Aim:

To evaluate the persistence of cognitive dysfunction in cirrhotics with/without prior OHE in an international, multi-center study.

Methods:

Cirrhotic patients with/without prior overt HE from 4 centers(2 US and 2 Italian) underwent cognitive testing with

(1) PHES: number connection test-A/B (NCT-A), digit symbol (DST), line drawing test (LTT errors/time) and serial dotting (SDT),

(2) Block design (BDT) and

(3) Inhibitory control test (ICT: outcomes are lures, targets and weighted lures(WL)) which has 2 identical halves.It is expected that patients without OHE would be able to learn and improve from the 1st to 2nd half, i.e. reduce lures/weighted lures and increase targets, but not those with prior HE. A high score on ICT Lures, NCT-A/B indicates poor cognition but opposite in the rest.

Results:

163 patients [age 59±8 years, education:12±3 years, 32 prior OHE (median 2 episodes; all on lactulose), 112 US & 51 Italian] were included. All prior OHE patients had normal MMSE (>25) and were similar to non-OHE patients on age (59 vs. 59 years, p=0.76) and education (11.8 vs. 12.9 years, p=0.18). Prior OHE patients were cognitively impaired compared to the rest (NCT-A: 65 vs 44, p=0.02,NCT-B:146 vs 102, p=0.01,DST: 32 vs 45, p< 0.0001, LTTtime: 130 vs 100, p=0.02, LTTerrors:49 vs 31, p=0.1, SDT:86 vs 74, p=0.2,BDT:13 vs 34, p< 0.0001, Lures: 16 vs 15, p=0.6,WL:31 vs 18, p=0.01,targets:77 vs 92%, p=0.001). Patients without prior OHE improved significantly on ICT from the 1st to 2nd half but those with prior OHE could not improve their performance indicating poor learning capability and persistent cognitive dysfunction (table); this trend was similar between countries.

*<0.0001 on Paired t-test	No OHE 1st Half	No OHE 2nd Half	Prior OHE 1st Half	Prior OHE 2nd Half
Lures	7.9±5.5	6.7±5.8*	8.4±5.5	7.7±5.3
Weighted lures	11±8	8±7*	18±13	15±14
Targets (%)	94.7±17.4	97.0±16.9*	75.7±29.4	76.7±29.1

[ICT learning in patients with/without prior OHE]

Conclusions:

Cirrhotics with prior OHE with normal MMSE exhibit persistent cognitive impairment that is not present in those without prior OHE . This persistence could have important implications for transplant listing and for prevention of the first episode.

COGNITIVE DYSFUNCTION IS ASSOCIATED WITH POOR SOCIO-ECONOMIC STATUS IN CIRRHOSIS IN AN INTERNATIONAL, MULTI-CENTER STUDY

STUDY O. RIGGIO[1], N. PIAZZA[1], E. ONORI[1], R. PRAKASH[2], S. ALLAMPATI[2], S. MONTAGNESE[3], P. AMODIO[3], K.D. MULLEN[2], N.A. NOBLE[4], M.B. WHITE[4], J.S. BAJAJ[4]*[1]CLINICAL MEDICINE, SAPIENZA UNIVERSITY OF ROME, ROME, ITALY, [2]GASTROENTEROLOGY AND HEPATOLOGY, CASE WESTERN RESERVE UNIVERSITY, CLEVELAND, OH, USA, [3]DEPARTMENT OF CLINICAL AND EXPERIMENTAL MEDICINE, UNIVERSITY OF PADOVA, PADOVA, ITALY, [4]GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION, VIRGINIA COMMONWEALTH UNIVERSITY AND MCGUIRE VA MEDICAL CENTER, RICHMOND, VA, USA. COGNITIVE DYSFUNCTION IN CIRRHOSIS IS NOT ROUTINELY INVESTIGATED. HOWEVER AN ASSOCIATION OF COGNITIVE PERFORMANCE WITH SOCIO-ECONOMIC STATUS COULD INCREASE ITS "REAL-WORLD" RELEVANCE TO CLINICIANS.

POSTER 612

Aim:

Study the association between cognition and socio-economic status in cirrhosis in an international, multi-center study.

Methods

Cirrhotics from 4 centers (2 US and 2 Italian) underwent testing with
(1) PHES: number connection test-A/B (NCT-A/B), digit symbol(DST), line drawing test (LTT errors/time) and serial dotting test (SDT) and
(2) Inhibitory control test (ICT: outcomes are lures/targets).
Local norms were used to adjudge abnormal performance. We inquired about the socio-economic status including income and employment using a validated questionnaire.

Results

140 patients (age 59±8 years, education 12±4 years, 20 prior HE, 98 US and 42 Italian) were included.

Only 50 patients(35%) were currently employed full/part-time. There was a significantly higher rate of unemployment in blue-collar rather than white-collar workers (44 vs. 26%,p=0.05). Employed subjects were significantly younger (55 vs. 60 years, p< 0.0001), better educated (13vs 11 yrs, p< 0.0001), had a better performance on all cognitive tests (NCT-A 34 vs. 54, p< 0.0001, NCT-B:76 vs. 128, p< 0.0001, DST:59 vs. 33, p< 0.0001, LTTt:89 vs. 111, p=0.002, LTTe:23 vs. 37, p=0.02, SDT: 58 vs. 83, p< 0.0001, lures:9 vs. 18, p< 0.0001, targets: 95 vs. 87%, p< 0.0001). Results were similar across countries. On logistic regression, the predictors of current employment were NCT-B(p< 0.0001), lures(p=0.01) and education(p=0.035).

Results (Cont'd):

Median annual personal income was between $16,000-25,000. If all assets were liquidated, patients would have $5000-9,999(median); if debt was subtracted from that, $500-4999 would remain. If all income was lost, the patient could only stay at their place between 3-6 months more; these were similar between US and Italy.

Income was correlated with education (0.37,p< 0.0001) but not age, and was higher in current workers($25,000-50,000 vs $12,000-16,000, p< 0.0001). It was significantly lower in those with abnormal NCT-B (p=0.05), lures (p=0.02), targets (p=0.03) and LTTt (p=0.02) but not the rest. On multi-variable regression, the significant predictors of income were employment (p< 0.0001), education (p=0.002), NCT-B (p=0.002) and ICT lures (p=0.047).

Conclusion

Socio-economic status in cirrhosis, represented by employment and personal income, is strongly associated with cognitive performance in this international, multi-center study.

AGREEMENT AND PREDICTIVE VALIDITY OF NEUROPHYSIOLOGICAL, PSYCHOMETRIC AND PSYCHOPHYSICAL INDICES OF HEPATIC ENCEPHALOPATHY (HE)

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POSTER 637

Background and Aims:

HE diagnosis and grading rely on neurophysiological, psychometric and psychophysical indices. The aim of this study was to investigate their degree of agreement and prognostic value.

Methods:

One-hundred-and-thirty-two cirrhotic outpatients were enrolled [94 males; 58±11 yrs; Child's class A:44, B:62, C:26; MELD: 13±5; 76/120 had a history of overt HE; 60/84 had portal-systemic shunt]. All underwent clinical assessment, EEG recording, paper-and-pencil psychometry (PHES) and Critical Flicker Frequency (CFF). The EEG was analyzed spectrally, PHES scored in relation to age/education-adjusted Italian norms and CFF deemed abnormal if ≤39 Hz. Seventy-nine patients were followed up prospectively for 11±7 months in relation to the occurrence of death/transplantation and HE.

Results:

On the day of study, 47(36%) patients had mild overt HE. Of these, 34 (72%) had abnormal EEG, 30 (64%) abnormal PHES and 20 (43%) abnormal CFF. Along the same lines, patients with overt HE had slower EEG (theta power: 43±17 vs. 26±17%, $p < 0.0001$), worse PHES score (-5.2±4.0 vs. -0.9±3.0, $p < 0.0001$) and worse CFF (40±5 vs. 42±5 Hz, $p < 0.05$) than their neuropsychiatrically normal counterparts. Of the 85 patients with no overt HE, 22 (26%) had abnormal EEG, 14 (16%) abnormal PHES and 26 (31%) abnormal CFF; 15 (18%) had more than one abnormal test. Patients with a history of HE had slower EEG (theta power: 37±19 vs. 25±16%, $p < 0.001$) and worse PHES score (-2.9±3.9 vs. -1.5±3.5, $p=0.05$) than their counterparts with negative history, while CFF was comparable in the two groups. Patients with portal-systemic shunt had slower EEG (delta power: 11±12 vs. 5±3%, $p < 0.05$) and a trend for worse PHES score (-2.6±3.8 vs. -1.3±2.8, $0.05 < p < 0.1$) than their counterparts with no shunt, while CFF was comparable in the two groups. During follow-up, 10 patients died, 10 were transplanted and 29 developed HE. The presence of overt HE ($p=0.004$), abnormal EEG ($p=0.008$) and abnormal PHES ($p=0.04$) at baseline predicted the subsequent occurrence of HE; CFF did not.

Conclusions

The agreement between neurophysiological, psychometric and psychophysical indices of HE is poor; the EEG seems to be more strongly associated with both previous and subsequent HE episodes.

LINKAGE OF GUT MICROBIOME WITH COGNITION IN HEPATIC ENCEPHALOPATHY

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Hepatic encephalopathy (HE) has been related to gut bacteria and inflammation in the setting of intestinal barrier dysfunction. We aimed to link the gut microbiome with cognition and inflammation in HE using a systems biology approach.

Multitag pyrosequencing (MTPS) was performed on stool of cirrhotics and age-matched controls. Cirrhotics with/without HE underwent cognitive testing, inflammatory cytokines, and endotoxin analysis. Patients with HE were compared with those without HE using a correlation-network analysis. A select group of patients with HE (n 7) on lactulose underwent stool MTPS before and after lactulose withdrawal over 14 days.

Twenty-five patients [17 HE (all on lactulose, 6 also on rifaximin) and 8 without HE, age 56 6 yr, model for end-stage liver disease score 16 6] and ten controls were included. Fecal microbiota in cirrhotics were significantly different higher Enterobacteriaceae, Alcaligeneceae, and Fusobacteriaceae and lower Ruminococcaceae and Lachnospiraceae) compared with controls. We found altered flora (higher Veillonellaceae), poor cognition, endotoxemia, and inflammation (IL-6, TNF-, IL-2, and IL-13) in HE compared with cirrhotics without HE. In the cirrhosis group, Alcaligeneceae and Porphyromonadaceae were positively correlated with cognitive impairment. Fusobacteriaceae, Veillonellaceae, and Enterobacteriaceae were positively and Ruminococcaceae negatively related to inflammation. Network-analysis comparison showed robust correlations (all P 1E-5) only in the HE group between the microbiome, cognition, and IL-23, IL-2, and IL-13. Lactulose withdrawal did not change the microbiome significantly beyond Fecalibacterium reduction.

We concluded that cirrhosis, especially when complicated with HE, is associated with significant alterations in the stool microbiome compared with healthy individuals. Specific bacterial families (Alcaligeneceae, Porphyromonadaceae, Enterobacteriaceae) are strongly associated with cognition and inflammation in HE.