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Members: Sharon Demorrow, PhD, Radhakrishnan Jayakumar, PhD, Robert Rahimi, MD, MSCR, Elliot Tapper, MD

P: 1 Junior Investigator | Oral Presentation

Genetic Fingerprint of Hepatic Encephalopathy Risk in Liver Cirrhosis
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BACKGROUND: To determine the impact of genetic factors on the development of hepatic encephalopathy (HE) in patients with liver cirrhosis.

METHODS: Patients suffering from compensated liver cirrhosis [n = 434; estimation cohort (n = 294) and validation cohort (n = 140)] were included. Patients were followed up for five years until HE bouts, liver transplant, or death. Methods: Patients were genotyped for 62 candidate SNPs (genes involved in the pathophysiology of HE: inflammation, ammonia and glutamine metabolism, intestinal barrier integrity and oxidative stress) by using OpenArray custom plates. Likewise, a haplotype formed by four SNPs within GLS plus the length of a microsatellite in the promoter region of GLS were determined (Romero-Gómez et al. Ann Intern Med 2010). Statistical analysis was performed by Cox regression and Kaplan-Meier for continuous and categorical data. Significant variables, and those known as weighted prognostic indicators, were entered into multivariable models by competing risks, according to Fine and Gray’s method.

RESULTS: In the estimation cohort, competing risks analysis showed GLS mutations, FUT2-(rs601338), TLR9-(rs5743836), SLC1A3-(rs2562582) and SLC1A5-(rs313853), together with MELD, albumin, sodium and previous episodes of HE as variables independently associated to HE development. Those genes encode for proteins involved in maintenance of intestinal barrier integrity by host-microbial interactions (FUT2), pro-inflammatory response triggered by pathogens (TLR-9) and glutamine transport (SLC1A3 and SLC1A5). Combining these genetic factors according to number of alleles at risk, three levels of risk patients were defined: low, mid or high risk [sHR: 1; 6.5 (1.8–22.9) P = 0.004, 27.1 (7.5–96.8) P < 0.001, respectively] (C-index = 0.82). This regression model performed in a similar manner in the validation cohort [sHR: 1; 4.2 (1.2–14.3) P = 0.024; 10.0 (2.7–36.7) P < 0.001] (C-index = 0.78). Cumulative survival free of HE after 5 years was also influenced by this genetic fingerprint: 95.3%, 77.0% and 42.5% for the low, mid and high-risk groups (log-Rank 53.1; P < 0.001) in the estimation, and 85.2%, 56.0% and 40.0% (log-Rank 14.1; P < 0.001) in the validation cohort, respectively (Figure 1).

CONCLUSIONS: Combination of unfavorable variants could predict HE. This genetic fingerprint could be implemented in clinical practice for decision making in the management of cirrhotic patients. Besides, this work emphasizes the role of these pathways in the pathophysiology of HE and brings out novel genes as potential therapeutic targets.

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Opioid Prescriptions Increase the Risk of Hepatic Encephalopathy in a National Cohort of Privately Insured Patients With Compensated Cirrhosis
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BACKGROUND: Hepatic encephalopathy (HE) is a common complication of cirrhosis associated with decreased quality of life and increased mortality. Opioids are commonly used to treat pain in patients with cirrhosis and may increase the risk of hepatic encephalopathy. In a population of patients with cirrhosis and no prior decompensation events, we aimed to assess whether opioids were associated with (1) HE and (2) other decompensation events (variceal bleed, hepatocellular carcinoma, ascites).

METHODS: We used the IMS PharMetrics database, which includes claims from >70 million privately-insured people in the United States, to identify patients aged 18–64 years with cirrhosis diagnosed from 1/1/2007 to 10/1/2015 based on the presence of two ICD-9 codes (571.2 or 571.3) on separate dates. We excluded patients with any decompensation event (defined by ICD codes,
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Uncovering Sex-based Differences in a Rat Model of Chronic Liver Disease and Hepatic Encephalopathy

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BACKGROUND: The impact of sex differences on chronic liver disease (CLD) and hepatic encephalopathy (HE) is unknown. The majority of animals used in research are male since the main difficulty with using female animals is the potential impact of the estrous cycle, increasing intragroup variability. The bile duct ligated (BDL) rat is a well-characterized model of CLD and HE in males which has not been investigated in females. Therefore, we aimed to characterize a female BDL model.

METHODS: Female BDL rats were compared to historical laboratory data from male BDL rats. The impact of sex differences in a Rat Model of Chronic Liver Disease and Hepatic Encephalopathy (CLD and HE) was evaluated.

RESULTS: Female BDL rats had increased liver enzymes (ALP (P = 0.005) compared to female shams. Whereas, male BDL rats have decreased fat mass, muscle circumference/weight and grip strength but had decreased albumin (P < 0.001), and decreased AST (P < 0.001) and ALT (P < 0.0001). Female BDL rats did not differ in body weight, muscle circumference/weight and grip strength but had decreased fat mass (P < 0.001), increased lean mass (P < 0.005) compared to female shams. Whereas, male BDL rats have decreased fat mass, muscle circumference/weight and grip strength. BDL in female rats induced a dysregulated estrous cycle compared to Sham (increased metestrus phase (P < 0.001)). Similar to male BDL rats, female BDL rats had increased anxiety (P < 0.005), motor incoordination (P < 0.05), and decreased night activity (P = 0.05) independent of the estrous cycle phase.

CONCLUSIONS: We demonstrated that BDL-induced impairment in females leads to hepatic and neurological impairment comparable to male BDL rats (similar intra-group variability). Interestingly, female BDL rats developed unique features. Contrary to male BDL vs. Shams, body weight and muscle mass does not differ between female BDL and Shams. Since muscle mass plays an important compensatory role in regulating ammonia levels, this could explain why the increase in blood ammonia levels in female BDL rats (vs. female Shams) was lower compared to male BDL. We expect that this model will provide new insights on the effect of sex differences on the pathogenesis of CLD and HE and help to personalize HE treatment.

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Let7i Expression Is Upregulated in the Frontal Cortex During Acute Liver Failure and Contributing to Hepatic Encephalopathy via Downregulation of TGFβ1 Expression

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BACKGROUND: Hepatic encephalopathy (HE) is a neurological complication that arises due to loss of liver function and is associated with increased blood-brain barrier (BBB) permeability, neuroinflammation and subsequent onset of cognitive decline. We have previously shown that increased circulating TGFβ levels induce BBB permeability and contribute to the development of HE. Associated with the aberrant TGFβ signaling during HE was an upregulation of the microRNA Let7i.
a known modulator of IGF1 expression in the brain. However, whether Let7f contributes to the development of HE is unknown. The aims of this study were to assess the expression of Let7f in a mouse model of Type A HE and to determine its involvement in the neurological complications of acute liver failure (ALF).

METHODS: C57Bl/6 mice were injected with azoxymethane (AOM) to induce ALF and HE. In parallel, mice were given an intracerebroventricular infusion of a Let7f antagonist or recombinant IGF1 (rIGF1) for 3 days prior to AOM injection. Cognitive impairment was monitored by reflex response assessment at various time points. Neuroumunclear deficits were assessed using a grip strength meter, and a digitag analysis system was utilized to measure ataxia. Liver damage was assessed by hematoxylin and eosin staining and serum chemistry. IGF1, Let7f and proinflammatory cytokine expression were assessed by immunohotstaining, immunohistochemistry and/or qPCR. Microglia were stained by IBA1 and cortex cytokine expression were assessed by immunoblotting, immunohistochemistry and/or qPCR. FRONT front cortex. Treatment with a Let7f antagomir attenuated the i) suppression of cortical IGF1, ii) The expression and secretion of IGF1 and the proinflammation, and iii) neurological and neuromuscular deficits of AOM-treated mice. Specific targeting of IGF1 expression by Let7f was demonstrated in vitro, where treatment of neurons with a Let7f mimic suppressed IGF1 expression and secretion. Furthermore, treatment of neurons with Let7f mimic increased the expression of CCL2, which could be attenuated with the co-treatment with rIGF1. Lastly, infusion of rIGF1 to restore the damped IGF1 signaling attenuated the neurological and neuroinflammatory deficits, as well as the neouromuscular observed in AOM-treated mice.

CONCLUSIONS: Elevated cortical Let7f expression contributes to the pathogenesis of HE in AOM-treated mice via mechanisms involving the suppression of IGF1 expression. These deleterious effects of Let7f during HE can be reversed by inhibiting Let7f expression or by increasing IGF1 concentration in the brain.

BACKGROUND: Patients with cirrhosis are growing older and the overlap between hepatic encephalopathy (HE) & pre-dementia mild cognitive impairment (MCI) is unclear. HE affects visuospatial/psychomotor speed while MCI affects memory. Aim: Determine the performance of elderly cirrhotics on tests for HE and dementia and their impact on quality of life (QOL).

METHODS: Outpatient cirrhotics and controls ages 65–95 years were recruited at 4 centers. Subjects had to have MMSE ≥ 25, no current HE or dementia to be eligible. All subjects got tests for HE (psychometric hepatic encephalopathy score, PHES: 5 tests & low score = poor, EncephalApp, OffTime + OnTime, high score = poor) and QOL (Sickness Impact profile, SIP, high score = poor QOL). Cirrhotics also got tests for MCI, RBANS (tests immediate memory, delayed memory, language, visuo-spatial & attention). A neuro-psychologist evaluated results and divided cirrhotics into (A) unimpaired (B) MCI only (C) HE only & (D) (MCI/HE overlap). Demographics, MELD, alcohol etiology, and SIP were compared. Finally, age, gender and education-adjusted norms were created for PHES and EncephalApp based on the controls. Presence of MHE and sensitivity of EncephalApp for MHE diagnosis were evaluated.

RESULTS: 199 cirrhotics and 100 non-cirrhotic subjects were included. Demographics/education levels were statistically similar between centers. Controls were older than cirrhotics (74.9 ± 6 vs 70.5 ± 4.4, P < 0.05) and had similar education/gender distribution. Despite this, controls performed better than cirrhotics on all tests (PHES 2.9 ± 12.4 vs 4.5 ± 4.5, P = 0.001, EncephalApp OffOn=181.4 ± 77.9 vs 218.2 ± 80.0, P = 0.03) and had a better QOL (SIP total 3.8 ± 7.1 vs 7.9 ± 9.5, Psych 3.1 ± 8.4 vs 7.2 ± 11.1, Phys 3.0 ± 6.2 vs 6.7 ± 9.5, all P < 0.001). Within cirrhotics subgroups (Table 1), demographics, MELD/alc & MMSE were similar. Pts with both MCI/HE had worse cognition on all tests, which translated into a worse QOL compared to other groups. Presence of HE, with/without MCI, contributed towards poor QOL. Norms for PHES/EncephalApp: Adjusting for age, gender & education, 17% (n = 17) patients were positive for MHE on PHES compared to controls. On EncephalApp, 49% (n = 47) patients were positive. AUC for EncephalApp using PHES as the gold standard was 0.86 (0.78-0.95 CI).

CONCLUSIONS: In this multi-center study, adjusted norms defining the high sensitivity of EncephalApp to diagnose HE in older individuals were created. Presence of HE regardless of MCI contributed towards poor cognition and QOL in patients >65 years.

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Interaction of Pre-dementia Mild Cognitive Impairment and Hepatic Encephalopathy in Elderly Patients With Cirrhosis: A Multi-Center Study

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Patients with cirrhosis are growing older and the overlap between hepatic encephalopathy (HE) & pre-dementia mild cognitive impairment (MCI) is unclear. HE affects visuospatial/psychomotor speed while MCI affects memory. Aim: Determine the performance of elderly cirrhotics on tests for HE and dementia and their impact on quality of life (QOL).

METHODS: Outpatient cirrhotics and controls ages 65–95 years were recruited at 4 centers. Subjects had to have MMSE ≥ 25, no current HE or dementia to be eligible. All subjects got tests for HE (psychometric hepatic encephalopathy score, PHES: 5 tests & low score = poor, EncephalApp, OffTime + OnTime, high score = poor) and QOL (Sickness Impact profile, SIP, high score = poor QOL). Cirrhotics also got tests for MCI, RBANS (tests immediate memory, delayed memory, language, visuo-spatial & attention). A neuro-psychologist evaluated results and divided cirrhotics into (A) unimpaired (B) MCI only (C) HE only & (D) (MCI/HE overlap). Demographics, MELD, alcohol etiology, and SIP were compared. Finally, age, gender and education-adjusted norms were created for PHES and EncephalApp based on the controls. Presence of MHE and sensitivity of EncephalApp for MHE diagnosis were evaluated.

RESULTS: 199 cirrhotics and 100 non-cirrhotic subjects were included. Demographics/education levels were statistically similar between centers. Controls were older than cirrhotics (74.9 ± 6 vs 70.5 ± 4.4, P < 0.05) and had similar education/gender distribution. Despite this, controls performed better than cirrhotics on all tests (PHES 2.9 ± 12.4 vs 4.5 ± 4.5, P = 0.001, EncephalApp OffOn=181.4 ± 77.9 vs 218.2 ± 80.0, P = 0.03) and had a better QOL (SIP total 3.8 ± 7.1 vs 7.9 ± 9.5, Psych 3.1 ± 8.4 vs 7.2 ± 11.1, Phys 3.0 ± 6.2 vs 6.7 ± 9.5, all P < 0.001). Within cirrhotics subgroups (Table 1), demographics, MELD/alc & MMSE were similar. Pts with both MCI/HE had worse cognition on all tests, which translated into a worse QOL compared to other groups. Presence of HE, with/without MCI, contributed towards poor QOL. Norms for PHES/EncephalApp: Adjusting for age, gender & education, 17% (n = 17) patients were positive for MHE on PHES compared to controls. On EncephalApp, 49% (n = 47) patients were positive. AUC for EncephalApp using PHES as the gold standard was 0.86 (0.78-0.95 CI).

CONCLUSIONS: In this multi-center study, adjusted norms defining the high sensitivity of EncephalApp to diagnose HE in older individuals were created. Presence of HE regardless of MCI contributed towards poor cognition and QOL in patients >65 years.
diagnostic codes have facilitated prior studies but are now invaded given the switch to ICD-10 in 2015. To date, no study has validated any diagnostic coding algorithm for HE using ICD-10 codes.

METHODS: From 2016–2017 at the University of Michigan outpatient liver clinic, we prospectively enrolled 300 persons with Child A–B cirrhosis and portal hypertension with no current or prior history of HE (60 patients were followed for up to 3 years). Each patient was assessed every 3 months for clinical developments (including new ON HE, falls, hospitalizations, and liver cancer) and recorded all medications taken. Over HE was defined as disorientation that was clinically defined as HE by the patient’s hepatologist. We surveyed all ICD-10 billing codes generated for each patient during follow up. We sought to evaluate the sensitivity and specificity of codes and medications for the presence of HE: K72.90 (hepatic failure), K72.91 (hepatic failure with coma), G93.40 (encephalopathy, NOS), G93.49 (Other encephalopathy), and prescription of lactulose or rifaximin.

RESULTS: Overall our cohort was aged 60 (52-66) years, 58.3% male, and 70% Child class A. All patients had portal hypertension, 76% had varices, and 41% had a history of ascites (predominantly well controlled). The median MELD-Na score was 9 (IQR, 7-13). Overall 68 out of 301 patients (22%) developed overt HE during follow-up. Only 1 patient was assigned the code K72.91, whereas codes G93.40 and G93.49 were not coded in our claims data. These 3 codes offered 0% sensitivity and specificity for HE. Conversely, the ICD-code K72.90 and high specificity (97.9%), positive predictive value (PPV) 84.8%, and negative predictive value (NPV) 85.1%. Recorded lactulose and or rifaximin use was highly sensitive (94.1%) and specific (98.3%), PPV 87.7%, NPV 98.3%.

CONCLUSION: In this prospective study, we define the performance of diagnostic codes for the identification of HE in the electronic health record study. Medications specific for HE therapy outperformed diagnostic codes.

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Assessment of Circitmic Patients With Covert Hepatic Encephalopathy (HE) Through the EnccephalApp (Stoop-Test) Based on Critical Flicker Frequency and PHES-Test

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BACKGROUND: In daily clinical practice, the detection of HE is still less represented but strongly required. Therefore, we assessed the EnccephalApp (Stoop-Test) in a German population by standard diagnostic procedures such as the Critical Flicker Frequency (CFF) and the PHES-Test (Psychometric Hepatic Encephalopathy Score). One of the purposes of the trial was finding a Cut-Off value for the EnccephalApp in the German population.

METHODS: 81 patients with liver cirrhosis underwent the testing of the CFF, the PHES-Test and the EnccephalApp. A control group of 25 healthy subjects were examined in the same manner. The CFF was considered pathological with <39 Hz and the PHES-Test with < -4 value points. The On-off-Off-Off Time of the PHES-Test was compared to the results of the CFF and the PHES-Test. Different Cut-Offs of the On-off-Off-Off Time were analyzed. Within these HE groups, the mean values of the PHES-Test, the CFF and the On-off-Off-Off Time of the EnccephalApp were compared and the ROC Analysis (receiver operating characteristic) was conducted. Laboratory parameters, clinical data, and further imaging techniques were also included and compared.

RESULTS: The study group (n = 81) included 52 men and 29 women (62.8 years ± 12.5). For the evaluation of the EnccephalApp, different Cut-Off values were determined and their specificity and sensitivity were calculated. The comparative parameter was the result of the PHES-Test. Through the creation of a ROC curve, the AUC (area under the curve) showed that the Cut-Off time of >224 sec with a specificity of 94% and a better sensitivity than the CFF (82%). Other Cut-Off values showed lower sensitivities and higher false negative values.

CONCLUSIONS: After evaluating the specificity, sensitivity and AUC the most efficient Cut-Off value for the On-off-Off-Off Time in the EnccephalApp is >224 sec. In comparison with the CFF and the PHES-Test, the On-off-Off-Off Time was most sensitive with better sensitivity (92%) and specificity (82%). Other Cut-Off values showed lower sensitivities and higher false negative values.

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Pharmacotherapies that Specifically Target Ammonia for the Prevention and Treatment of Hepatic Encephalopathy in Adults With Cirrhosis

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BACKGROUND: Ammonia plays a key role in the genesis of hepatic encephalopathy (HE). Recent interest has focused on drugs which specifically target ammonia, e.g. sodium benzolate (SB), glycolate phenylbutyrate (GPB), ornithine phenylacetate (OP), AST-120, and polyethylene glycol (PEG). This study aims to evaluate the utility of these pharmacotherapies vs placebo or non-absorbable disaccharides (NAD), for the management of HE in people with cirrhosis. L-ornithine L-aspargine is not included.

METHODS: Electronic/manual searches of the literature were undertaken for relevant RCTs. The results of the meta-analyses are presented as risk ratios (RR) or mean differences (MD) with 95% confidence intervals (95% CI). Meta-analysis was performed using the Cochrane tools and the certainty of evidence using GRADE.

RESULTS: Eleven RCTs were identified involving SB (n = 1), GPB (n = 1), OA (no n = 2), AST-120 (n = 2) and PEG (n = 3). Treatment periods ranged from five days to 16 weeks. All but one trial was at "high risk of bias"; the certainty of the evidence was very low for all outcomes. Nine trials, with 733 participants, reported blood ammonia concentrations. Significant reductions were observed in placebo-controlled trials evaluating SB (MD = −32.00, 95% CI = −46.85 to −17.15), GPB (MD = −12.00, 95% CI = −23.37 to −0.63), OP (MD = −27.10, 95% CI = −48.55 to −5.65) and AST-120 (MD = −22.00, 95% CI = −26.75 to −17.25). No significant differences in blood ammonia concentrations were observed when compared to NADs. Eleven trials, with 943 participants, reported mortality data, although there were no events in five trials. No beneficial or harmful effects were found in any of the trials. Seven trials, with 521 participants reported data on HE. Beneficial effects were identified for GPB vs placebo (RR 0.57, 95% CI 0.36 to 0.90, 178 participants, 1 trial; NNTB = 6) and for PEG vs. lactulose (RR 0.19, 95% CI 0.08 to 0.44, 190 participants, 3 trials; NNTB = 4), no beneficial effects were observed in the remaining three trials with extractable data (Figure 1). Ten trials, with 790 participants, reported a total of 150 serious adverse events. There was no evidence of beneficial or harmful effects of the five agents when compared to placebo NAD.

CONCLUSIONS: These agents generally reduce blood ammonia concentrations, when compared to placebo, but not when compared to NADs. Their overall effects on clinical outcomes of interest and the potential harms associated with their use remain uncertain. Further evidence is needed to fully evaluate their utility in this clinical setting.
analyzed cognition (EncephalApp high = worse) at baseline and 30 days post-intervention (Figure 1a red arrows). Stool microbiota was analyzed using 16s rRNA & BAs using LC/MS. Fecal BA moieties analyzed were (a) total (b) primary (c) secondary (d) deconjugated (e) tertiary BAs. Secondary/primary BA ratios were calculated. Serum was also analyzed for lipopolysaccharide-binding protein (LBP) & IL-6. Analyzed were (a) total (b) primary (c) secondary (d) deconjugated (e) tertiary BAs. Secondary/primary BA ratios were calculated. Serum was also analyzed for lipopolysaccharide-binding protein (LBP) & IL-6. Analyzed were (a) total (b) primary (c) secondary (d) deconjugated (e) tertiary BAs. Secondary/primary BA ratios were calculated. Serum was also analyzed for lipopolysaccharide-binding protein (LBP) & IL-6. Analyzed were (a) total (b) primary (c) secondary (d) deconjugated (e) tertiary BAs. Secondary/primary BA ratios were calculated. Serum was also analyzed for lipopolysaccharide-binding protein (LBP) & IL-6.

RESULTS: All subjects completed the follow-up without any serious AEs related to FMT/placebo. EncephalApp total score (P < 0.05) improved in FMT pts only. Microbiota: there was a significant enrichment of donor microbiota with higher Ruminococcaceae & Lachnospiraceae in stool/duodenum in FMT pts. Inflammation/translocation. A reduction in LBP & IL-6 was seen only in FMT pts (Figure 1b,d). BAs: There was a significant increase in secondary/primary BA ratio (Figure 1c) in FMT pts. Deconjugation and tertiary BAs remained similar between groups. Correlation network complexity was compared between post-FMT vs post-placebo states.

CONCLUSIONS: Capsular FMT is safe and improves cognition in pts with cirrhosis and HE compared to placebo. These improvements are associated with beneficial changes in microbial composition and function and differential correlations with bacterial translocation and inflammation.
Table 1: Psychometric test results of all patients subdivided by history of hepatic encephalopathy compared to adjusted healthy controls 9 months (T2) and 5 years (T3) after LT

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=55/test)</th>
<th>HE (n/test)</th>
<th>NHE (n/test)</th>
<th>p value</th>
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<tbody>
<tr>
<td>T2</td>
<td></td>
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<tr>
<td>PHES (25th; 75th Percentile)</td>
<td>1 (0.2)</td>
<td>0 (-2.1)</td>
<td>0.5 (-1.2)</td>
<td>&lt;0.01*</td>
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<td></td>
<td></td>
<td>(n=37)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS T5 (means/SD)</td>
<td>99.9 ±12.0</td>
<td>89.5 ±15.6</td>
<td>94.4 ±12.5</td>
<td>&lt;0.01*</td>
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<td></td>
<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS Sumscore (means/SD)</td>
<td>500.9 ±39.9</td>
<td>483.5 ±57.2</td>
<td>480.8 ±45.9</td>
<td>0.001*</td>
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<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS Attention (25th; 75th Percentile)</td>
<td>103 (94;112)</td>
<td>88.5 (79;103)</td>
<td>98.5 (85;108.6)</td>
<td>0.001*</td>
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<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS Delayed Memory (25th; 75th Percentile)</td>
<td>99 (94;106)</td>
<td>98 (91;104.5)</td>
<td>97.5 (94.8;102)</td>
<td>0.41</td>
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<td></td>
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<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS Visuospatial/Constructional (25th; 75th Percentile)</td>
<td>89 (81;105)</td>
<td>84 (73.5;102)</td>
<td>85.5 (77.3;102)</td>
<td>0.42</td>
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<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS Immediate Memory (25th; 75th Percentile)</td>
<td>108 (94;112)</td>
<td>88.5 (81.5;106)</td>
<td>95.5 (86;109.8)</td>
<td>0.001*</td>
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<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>RBANS Language (25th; 75th Percentile)</td>
<td>101 (96;106)</td>
<td>101 (87.3;106)</td>
<td>99 (93.5;110.5)</td>
<td>0.64</td>
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<td>(n=36)</td>
<td>(n=30)</td>
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<tr>
<td>CGF (25th; 75th Percentile)</td>
<td>44.4 (41.8;46.9)</td>
<td>42.7 (39.8;44.35)</td>
<td>42.4 (41.3;46.2)</td>
<td>0.04*</td>
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<td>(n=33)</td>
<td>(n=29)</td>
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<td>ICT Targets (%) (25th; 75th Percentile)</td>
<td>98.58 (96.7;99.5)</td>
<td>97 (92.98)</td>
<td>97 (96.99)</td>
<td>0.03*</td>
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<td>(n=35)</td>
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<td>T3</td>
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<tr>
<td>PHES (25th; 75th Percentile)</td>
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[10]
The Role of Monocarboxylate Transporter-1 and Lactate Metabolism on the Development of Cognitive Deficits During NAFLD

Anna Hadjihambi, PhD1, Patrick S Hosford, PhD2, Rajiv Jalan, PhD, MD3,4,5, Luc Pellerin, PhD1.

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is a major complication of obesity. Certain observations regarding NAFLD-induced neuropsychiatric and neurochemical alterations have been reported but mechanisms are unknown (Seo, 2016). In this context, mono-carboxylate transporter-1 (MCT1) haploinsufficient mice, which resist high fat diet (HFD) induced hepatic steatosis represent an interesting model (Carneiro, 2017). Using a mouse model of NAFLD (HFD high fructose/high glucose in water [HF/HG]) we investigated the development of cognitive deficits and state of cerebral oxygenation and cerebrovascular reactivity.

METHODS: Behavioural tests (open field/novel object recognition/forced swimming test [FST]) were performed in mice fed control diet (NC; WT + NC, MCT1 ± + NC) or HFD HF/HG (WT + HFD HF/HG, MCT1 ± + HFD HF/HG) for 16 weeks. Baseline PO2 (in somatosensory cortex) and in response to systemic hypercapnia (10% CO2) was monitored under anaesthesia by a fluorescence method (Oxylite). Microelectrode biosensors were used for measurements of lactate release by cortical slices. EchoMRI was performed to assess lean/fat mass.

RESULTS: Increased fat mass (not lean mass) was observed in WT and MCT1 ± mice (50% less) on HFD HF/HG compared to NC controls. Liver mass was only significantly higher in WT ± HFD HF/HG mice compared to NC controls. Behavioural tests did not reveal any significant differences between groups except for FST, which indicated a depression-related behaviour in the WT ± HFD HF/HG group compared to their controls. This was not observed with MCT1 ± HFD HF/HG mice. WT ± HFD HF/HG mice had a lower cerebral PO2 baseline and PO2 response induced by systemic hypercapnia compared to NC controls although significance was not reached, while the MCT1 ± groups remained unchanged. Tonic lactate release was unaltered between all groups although the MCT1 ± HFD HF/HG group indicated a trend of decreased lactate tone.

CONCLUSIONS: Our results suggest that NAFLD is associated with a depression-related behaviour and a trend of decreased cerebral PO2 baseline. MCT1 haploinsufficient mice were resistant to the reported phenotypes, suggesting a link between liver metabolism and neuropsychopathological alterations in NAFLD.

SD standard deviation, n number, HE Hepatic Encephalopathy, NHE No hepatic Encephalopathy, n number, SD standard deviation, PHES hepatic encephalopathy score, RBANS Repeatable Battery for the Assessment of Neuropsychological Status, TS Total Scale, CFF Critical Flicker Frequency, ICT Inhibitory Control Test, vs. versus, Con Controls, t1 before transplantation, t2 9 months after transplantation, t3 5 years after transplantation, *overall between groups, P value ≤ 0.05 is considered significant

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Non-alcoholic Fatty Liver Disease Alters Expression of Genes Governing Hepatic Nitrogen Conversion

Peter Lykke Eriksen, MD, PhD1, Hendrik Vilstrup, Professor, MD, DSc1, Kristoffer Righolt, Principal scientist2, Malte Palm Suppli, MD3, Michael Sørensen, MD, PhD1, Søren Skovgaard Veidka, Group leader2, Filip Krag Knop, Professor, MD, PhD3, Karen Louise Thomsen, MD, PhD1.

1Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; 2Gubra, Hørsholm, Denmark; 3Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark.

BACKGROUND: We recently showed that the functional capacity for ureagenesis is deficient in patients with NAFLD. The aim of this study was to assess the expression of urea cycle and related genes to elucidate whether there may be a gene regulatory basis to the functional problem.

METHODS: Liver mRNA expression analyses within the gene pathway governing hepatic nitrogen conversion were performed in 20 non-diabetic, biopsy-proven NAFLD patients (8 simple steatosis; 12 non-alcoholic steatohepatitis (NASH)), and compared with 12 obese and 14 lean healthy control persons. The relationship between gene expressions and functional capacity for ureagenesis was described.

RESULTS: Gene expression of most urea cycle-related enzymes were downregulated in NAFLD vs. both control groups and markedly so for the urea cycle flux-generating carbamoyl phosphate synthetase (CPS1) (3.5-fold, \( P < 0.0001 \)). In the NASH patients, the reduction of CPS1 expression paralleled the deficit in functional ureagenesis (\( P = 0.03 \)). Additionally, the expression of several genes involved in amino acid uptake and degradation, and the glucagon receptor gene, were downregulated in NAFLD. Conversely, gene expression of glutamine synthetase (GS) increased more than 1.5-fold (\( P < 0.03 \)), inversely related to CPS1 expression (\( P = 0.004 \)).

CONCLUSIONS: NAFLD downregulated the expression of urea cycle-related genes. Downregulation of the urea cycle flux-generating enzyme CPS1 correlated with loss of functional capacity for urea synthesis in patients with NASH. On gene level, these changes coincided with an increase in the major ammonia scavenging enzyme GS. The effects seemed to be related to a fatty liver as such rather than NASH or obesity. The findings support that gene regulatory mechanisms are involved in the deficient urea synthesis of NAFLD, but it remains unexplained how the hepatocyte fat accumulation exerts these
Results: Groups were matched for age, sex, baseline educational level, weekly alcohol consumption, baseline PHE score, CogstateTM computerized psychometric testing, WTAIR and SF36 scores. Color-naming subset of the Stroop task was significantly impaired at baseline in LOLA receivers (P = 0.0179) For group averaged whole-brain data, there was no significant difference in activation for both motor and cognitive tasks or in resting state in all 34 patients at baseline and 12 weeks. Group differences by region of interest (see Table 1 below) the choice reaction time task in the default mode network (DMN) demonstrated significant treatment (P = 0.0262) advantage after 12 weeks of LOLA. Of the 12 resting state networks studied, visual area 2 showed a significant treatment (P = 0.0211) benefit after 12 weeks of LOLA.

Conclusion: In the first RCT of LOLA combined with modern brain imaging analysis, a significant treatment benefit with LOLA on task activation was noted in the DMN. A significant treatment advantage of LOLA on resting-state fMRI in the visual network is consistent with this, this may be a compensatory mechanism in early MHE. Future studies could stratify patients who may benefit from LOLA based on base-line fMRI characterisation.

P: 16 Junior Investigator | Oral Presentation

Traditional Prognostic Tools are Superior to Cognitive Testing and Stool Frequency as Predictors of Poor Outcomes in Cirrhotic Patients Admitted with Hepatic Encephalopathy

Patricia Pringle Bloom, MD1, 
1Massachusetts General Hospital, Boston, MA, USA.

BACKGROUND: Model for end-stage liver disease-sodium (MELD-Na) score and extrahepatic organ failures (EHOFs) predict poor outcomes in cirrhotic patients, including those with hepatic encephalopathy (HE); however, there is a need for the development of additional and specific predictors for outcomes in HE. We aimed to determine if cognitive testing, total daily lactulose dose (TDDL), and stool frequency at hospital discharge predicts readmission and other poor outcomes in patients admitted with overt HE.

METHODS: We performed a prospective study of patients admitted to a single transplant center with overt HE. When the primary team anticipated discharge within 48 hours, consented subjects underwent Psychometric HE Score (PHE), Montreal Cognitive Assessment (MOCA), liver futility index (LFI), and stool frequency assessment. MELD-Na, EHOFS, and other clinical variables were assessed via chart review. At 30 days post-discharge, subjects were called to evaluate for a composite primary outcome of HE readmission, transition to hospice, liver transplantation, or death. T-test or chi-square test compared predictors between those who did and did not meet the primary endpoint.

RESULTS: Of 175 potential candidates, 32 patients provided informed consent and enrolled, with the majority (82) of patients excluded for discharge, death, transplant, or transfer to hospice before enrollment could be performed. Within 30 days, 7 patients had a readmission for HE, and 11 died, were transplanted or transferred to hospice. Seventeen patients met the primary composite endpoint. MELD-Na (28.1 ± 8.0 vs. 22.0 ± 6.0, P = 0.01) and the number of EHOFS (1.3 ± 1.3 vs. 0.5 ± 0.8, P = 0.03) were higher in patients who met the primary composite outcome. Most predictors did not vary between those who met and did not meet the primary endpoint, including MOCA score (P = 0.73), PHE score (P = 0.97), stool frequency (P = 0.34), total daily lactulose dose (P = 0.80), LFI (P = 0.57), admission ammonia (P = 0.58), or being discharged on rifaximin (P = 0.70). Stool frequency at discharge did not correlate with PHE (P = 0.71) or MOCa score (P = 0.51).

CONCLUSIONS: Traditional prognostic tools in cirrhosis, including MELD-Na and EHOFS, were superior to cognitive assessments, total daily lactulose dose, and stool frequency in predicting 30-day outcomes for those admitted with overt HE. Future studies should evaluate MELD-Na and the presence of EHOFS as determinants of discharge readiness or discharge destination in patients admitted with cirrhosis and HE.
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Total
| Grand Total | 2290.38 | -594.51 | 2211.76 | 1496.97 | -943.62 | 1665.08 |
RESULTS: A total of 187 patients with a diagnosis of cirrhosis were approached for recruitment in the trial. 98 patients were excluded, whilst 17 patients declined. A total of 72 participants were enrolled in the trial. 37 participants had MHE whilst 35 participants did not have MHE. 16 participants had sarcopenia and MHE, whilst 18 participants had sarcopenia with no MHE. Over the average two year follow up, participants who did not have MHE and were not sarcopenic did not develop overt hepatic encephalopathy. Whilst participants with MHE and Sarcopenia had a significantly higher risk of developing OHE and mortality as can be seen in Figure 1 F value <0.05. The Stroop test had the highest sensitivity (79% [CI 47%–86%]) whilst the CFF had the highest specificity (78% [CI 66%–87%]) F value 0.005. In the subset analysis of patients who underwent a DEXA scan to assess lean body mass, this was not able to predict the risk of developing OHE.

CONCLUSIONS: MHE and Sarcopenia assessment can be easily completed as a bedside clinical test to predict the long-term risk of mortality and the development of overt hepatic encephalopathy.

P: 18 Junior Investigator

Impaired Cerebral Oxygenation, but Preserved Cerebrovascular Reactivity, in an Animal Model of Hepatic Encephalopathy

Anna Hadjihami, PhD1,2, Patrick S. Hoford, PhD3, Abeba Haltecto2, Nathan Davies, PhD2, Alejandro Y. Gourine, PhD2, Rajiv Jalan, PhD2, MD2.
1University de Lausanne, Department of Physiology, Lausanne, Switzerland; 2UCL Institute for Liver and Digestive Health, Division of Medicine, University College London Medical School, Royal Free Hospital, London, UK; 3Centre for Cardiovascular and Metabolic Neuroscience, Neuroscience, and Digestive Health, Division of Medicine, University College London Medical School, Royal Free Hospital, London, UK.

BACKGROUND: We have recently obtained evidence of energy deficiency, in the form of impaired lactate release, in the brains of cirrhotic animals with hepatic encephalopathy (HE). Previous reports of cerebral hyperperfusion in patients with HE indicated that cerebral oxygen supply could also be compromised (Dam et al., 2013). Decreased lactate and reduced oxygen supply may lead to CNS energy deficiency and have important neurological consequences, particularly in patients with advanced cirrhosis. In this study we assessed cerebral tissue oxygen tension and CO2 cerebrovascular reactivity in an animal model of HE.

METHODS: HE was induced by bile duct ligation (BDL) and after 4 weeks rats were anesthetized with α-chloralose (100 mg·kg−1), instrumented for arterial blood pressure recording and artificially ventilated. 7 BDL and 6 sham-operated animals were treated daily for one week with an ammonia lowering treatment, ornithine phenylacetate (OP) in order to investigate the role of ammonia on brain oxygenation. Blood gas tensions and pH were maintained within physiological ranges in all animal groups. Cerebral tissue PO2 was monitored by fluorescence method (Oxylite®). After a small craniotomy, optical sensors were placed in the somatosensory cortex and sealed. PO2 at baseline and in response to systemic hypercapnia (10% CO2, 5 min) was recorded.

RESULTS: BDL resulted in high plasma ammonia concentrations which was lowered with OP treatment. At similar levels of blood PO2 and PCO2, BDL rats had a significantly lower brain PO2 (15.3 ± 2 mm Hg, n = 10) compared to sham controls (26 ± 2 mm Hg, n = 6; P = 0.001). BDL rats treated with OP showed a significant improvement in cerebral PO2 (22 ± 1 mm Hg, n = 6; P = 1), increasing the oxygen tension to levels similar to that recorded in OP treated sham rats (27 ± 2 mm Hg, n = 7), when blood PO2 and PCO2 were constant. Systemic hypercapnia resulted in similar increases in cerebral PO2 in BDL and sham-operated animals (ΔPO2 21 ± 2 vs. 24 ± 2 mm Hg, P = 0.6). Additionally, under anaesthesia, the mean systemic arterial blood pressure was found to be significantly lower in BDL animals (60 ± 3 vs. 84 ± 8 mm Hg, P = 0.04). Cerebral oxygenation did not recover when the blood pressure was normalised via infusion of phenylephrine, but it significantly improved with infusion of acetazolamide which increases cerebral blood flow.

CONCLUSIONS: In the BDL model of HE, cerebral tissue oxygen tension is compromised but cerebrovascular reactivity to CO2 appears to be preserved. The cause of the low basal PO2 remains unknown however; high ammonia concentrations and hyperperfusion could be contributing factors.
P: 20 Junior Investigator

EID-UL-AZHA (Muslim’s Festival of Sacrifice): Increased Frequency of Spontaneous Encephalopathy, Whether This Is Secondary to Consumption of High Protein Diet? Rahmatullah Bhatti1.

BACKGROUND: Protein restricted diet once was the cornerstone of the management of Hepatic encephalopathy, latter no evidence showed significant benefit. However sub group of cirrhotics are intolerant to dietary proteins, especially animal proteins. We compared precipitants of encephalopathy and effect of animal proteins consumption during the festival of EID-UL-AZHA

METHODS: A retrospective comparative cross sectional study was conducted and analyzed hospital data of AIMS (Asian Institute of medical sciences, Hyderabad, Pak.). Patients of cirrhosis were enrolled with clinically diagnosed hepatic encephalopathy in two groups. Group A was categories with patients admitted 15 days before EID-UL-AZHA and Group B includes patients admitted on EID UL AZHA day and up to 15 days afterward. Patients with neurological deficit and suspected CNS infection were excluded. Patients of both groups were assessed to compare precipitant factors for encephalopathy that includes infections, electrolytes imbalance, upper GI bleed, constipation, AKI and drugs. Dietary history regarding normal protein diet and high protein diet (animal proteins > 1.5 g/kg/day) were also collected and compared in both groups.

RESULTS: Out of 576 screened patients, 92 were presented with encephalopathy. All patients were Muslims with mean age 54.56 ± 11 yrs. Majority 66.3% were males and 33.7% were females. Precipitating factors were identified in 70.2% and 62.9% in group A and B respectively. Precipitating factor remain unidentified in 29.8% patients in group A and 37.1% in group B. 98.2% patients in group A were taking usual diet, only 1.8% consumed high (animal) protein diet, while in group B 51.4% patients were on usual diet and 48.6% consumed high (animal) protein diet. A comparable rise in frequency of spontaneous hepatic encephalopathy (without an identified precipitating factor) was observed in group B and 76.9% patients out of them were consuming high (animal) protein diet.

CONCLUSIONS: A comparable rise in frequency spontaneous hepatic encephalopathy was observed during and/or post event of EID-UL-AZHA, majority had consumed high (animal) proteins. Consumption of meat (animal proteins) could be the possible contributing factor. Generally protein restriction is not recommended in cirrhotics but, still in sub group of cirrhotics who are protein intolerant, protein restriction or substitution of source of protein is inevitable. A further multicenter study is necessary at a larger scale to find out characteristic of patients who are intolerant to animal proteins.

P: 21 Junior Investigator

Changes in Cerebral Hemodynamic Parameters in Patients With Acute Liver Failure Juanita Pérez, MD1, Viridiana López, MD2, Carlos Cantú, MD2, Fernanda Flores, MD2, Aldo Torres, MD1.

1National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico.

BACKGROUND: Acute liver failure (ALF) is a clinical syndrome that results from severe and sudden failure (AHF). Transcranial Doppler ultrasound (TCD) is a non-invasive device that can continuously measure the speed of cerebral blood flow, producing a velocity-time waveform that indirectly monitors cerebral hemodynamics, making it very useful in patients with ALF. Objetives Compare the cerebral hemodynamic parameters in patients with ALF before and after liver transplantation.

METHODS: A retrospective comparative cross sectional study was conducted and analyzed hospital data of AIMS (Asian Institute of Medical Sciences (AIMS), Hyderabad, Pakistan).

RESULTS: A and 10% pharmacological. We identified 4 deaths, 1 of which was during the post-transplant period. The following parameters were measured: systolic peak velocity (SPV), final diastolic velocity (F DV), medium velocity of the middle brain artery (VM), resistance index (RI) and pulsatility index (PI). There were changes in RI and PI, before transplant TDC: RI 0.69 (0.58–0.71) PI 1.29 (0.96–1.37) and after transplant TDC RI 0.51 (0.40–0.58); PI 0.78 (0.55–0.93) P value = 0.005 and 0.005 respectively.

CONCLUSIONS: There was a significant decrease in the rates of pulsatility and resistance after liver transplantation.

REFERENCES

P: 22 Junior Investigator

Deficit of Short Working Memory in Rat With Thioacetamide-Induced Progressive Acute Hepatic Encephalopathy Involving Serotonin Innervation and Astroglia Dysfunctions A. El Khiat, Student, PhD1, O. El Hiba, PhD2, Mohamed Aitihya, Student, PhD1, L. Tamegart, Student, PhD1, A. Draoui, Student, PhD1, R. El Fari, Student, PhD1, H. Giamei, PhD1, 1Asian Institute of Medical Sciences (AIMS), Hyderabad, Pakistan.

BACKGROUND: Hepatic encephalopathy (HE) is defined as the whole neurological and neuropsychiatric disorders arising from both acute and chronic liver failures. Patients with chronic HE exhibited an impairment of learning and memory abilities as well as attention. The aim of the present study is to evaluate the progression of short working memory alteration in acute HE and to delineate the glial and the neuronal alterations which may underlie such cognitive impairment.

METHODS: The study was performed in Sprague-Dawley rats with acute liver failure induced by thioacetamide (TAA) at a dose of 300 mg/kg i.p. Different stages of acute HE was defined as: 12, 24h and 36h following administration of TAA. Working memory was assessed by the T-Maze test via the percentage of alternation behavior, as well, an immunohistochemical analysis of GFAP in the hippocampus and serotonin (5-HT) within the dorsal Raphe nucleus (DRN).

RESULTS: Our data showed a progressive loss of the alternation behavior, which was accompanied by a time dependent and region-specific changes of GFAP-immunoreactive astrocytes within the hippocampus together with a reduced 5-HT immunoreactivity within the DRN.

CONCLUSIONS: Our data revealed for the first time, a progressive loss of short memory function in acute HE, resulting from acute liver dysfunction which may involve a possible glialopathy as well as a 5-HTergic dysfunctions.

P: 23 Junior Investigator

Prospective Study on Mortality of Acute on Chronic Liver Failure and Its Predictors Rahmatullah Bhatti1.

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BACKGROUND: Acute on chronic liver failure (ACLF) is a well recognized entity, characterized by an acute liver insult in patients with underlying chronic liver disease leading to sudden deterioration of liver function and a high mortality. We aimed to determine hospital, 28 days and 12 weeks mortality of ACLF; its predictors and precipitating factors

METHODS: We conducted a prospective descriptive study at AIDS (Asian institute of medical sciences, Hyderabad, Pak.) from January 2018 to December 2018. We enrolled patients of ACLF as defined by Asian Pacific Association for the Study of Liver (APASL, 2014) and collected data to determine cause, precipitating acute insult, organ failure, ACLF grade, encephalopathy, MELD score and AKI scores. Patients were followed to determine hospital, 28 days and 12 weeks mortality and its predictors.

RESULTS: Total patients were 117 with mean age of 40.9 ± 13.9 years (range 12–85). Majority were males (73.5%) and 31 (26.5%) were females. Majority of patients 55 (47%) were Hepatitis B Virus (HBV) positive, among them 24 (43.6%) were with HDV co-infection. The most common precipitating acute insult was SEPSIS 65 (55.6%). Others were drug induced liver injury (DILI) 8 (6.8%), HEV acute hepatitis 7 (5.9), HDV superinfection 5 (4.3%), HBV flare 4 (3.4%), alcohol binge drinking 4 (3.4%), surgery 2 (1.7%), acute PVT 2 (1.7%), Upper GI bleed 1 (0.9%) and 20 (17.1%) were unknown. Hospital mortality was 49 (41.9%), 28 days 71 (60.7%) and 12 weeks mortality was 103 (88.0%). Organ failure (P = 0.002), ACLF grade (P = 0.001), encephalopathy (P = 0.001), MELD (P = 0.01) and AKI (P = 0.02) were found to be predictors of mortality.

CONCLUSIONS: Acute-on-chronic liver failure (ACLF) is an acute deterioration of liver function superimposed on Chronic Liver Disease with a high mortality. In our study HBV infection was the most common cause of ACLF, and sepsis was the commonest acute insult. We found high hospital, 28 days and 12 weeks mortality. Organ failure, ACLF grade, encephalopathy, MELD score and AKI were found to be predictors of mortality of ACLF.

P: 24 Junior Investigator

Comparative Morphological Analysis of Astroglia Reactivity in the Hippocampus of Rats With Acute and Chronic Hepatic Encephalopathy

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1Chouaib Doukkali University, El Jadida, Morocco; 2Cadi Ayyad University, Marrakech, Morocco.

BACKGROUND: Hepatic encephalopathy (HE) is a serious complication of advanced liver failure which represents the whole neuropsychiatric abnormalities resulting from liver disease ranging from abnormal behavior to coma. Impairment of cognitive function is well described in HE patients, while mechanisms of memory impairment in HE patients is still not fully understood, however, it may involve a possible gliopathy as well as neuroplasticity in various brain areas, including the hippocampus known as the main brain structure associated to the memorization process. The aim of the present investigation is to assess astroglia reaction of the hippocampus, in a comparative approach between acute and chronic HE in rat.

METHODS: Sprague-Dawley rats were divided into 3 groups: controls, rats were treated with saline solution (NaCl 0.9% i.p) during 3 days, chronic HE group: rats were subjected to bile duct ligation and acute HE group: rats were subjected to 3 ip injections of thioacetamide (TAA) 300 mg/kg BW.

Results: Our data showed in the TAA rats (3 days following 3 TAA injections) compared to controls, a significant increase of GFAP immunoreactivity within the whole hippocampal areas, while astrogial processes length and ramification were reduced, the GFAP immunoreactive area was increased. In contrast to BDL rats, at the cirrhotic stage (4 weeks after surgery), showing the opposite trend with a drop of the astrocytic GFAP-immunoreactive area as well as the astrogial length and ramification levels.

CONCLUSIONS: The present finding sustains a differential astroglial reactivity within the hippocampus of acute and chronic HE rats. Astrocytic morphology changes depends to the severity of liver failure and seems to HE type-dependent, while those astrogial changes lead to a severe gliopathy which may be behind the disturbed cognitive function, especially memory seen in patients with chronic as well as acute HE.

P: 25 Junior Investigator

Muscle Alterations Are Associated With Minimal and Overt Hepatic Encephalopathy in Patients With Liver Cirrhosis

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2European Institute of Oncology, Milan, Italy.

BACKGROUND: Muscle alterations (myosteatosis and sarcopenia) are frequent in cirrhosis and related to some complications included overt hepatic encephalopathy. The aim of our study was to investigate the relationship between muscle alterations and minimal hepatic encephalopathy (MHE) and their role on the risk of overt HE.

METHODS: 64 cirrhotics were submitted to Psychometric Hepatic Encephalopathy Score (PHES) and to Animal Naming Test (ANT) to detect MHE. CT scan was used to analyse the skeletal muscle index (SMI) and attenuation. The incidence of the first episode of HE, taking into account the competing risk nature of the data, was estimated.

RESULTS: Myosteatosis was observed in 24 patients (37.5%), sarcopenia in 37 (58%) and MHE in 32 (50%). Both myosteatosis (62.5 vs 12.5%, P < 0.001) and sarcopenia (84 vs 31%, P < 0.001) were more frequent in patients with MHE. The variables independently associated to the presence of MHE were: sarcopenia, previous overt HE and myosteatosis. Thirty-one (48%) patients developed overt HE during 16 ± 13 months; myosteatosis was detected in 68% and sarcopenia in 84% of them. Sarcopenia and myosteatosis were also independently associated to the development of overt HE. Venous ammonia was significantly higher in sarcopenic patients (62.6 ± 17.7 vs 41.4 ± 16.1 μg/dl, P < 0.001) and in myosteatosis patients (65.2 ± 19.2 vs 46.7 ± 17.1 μg/dl, P < 0.001) and inversely correlated to both parameters. Survival was significantly lower in malnourished patients compared with patients without myosteatosis or sarcopenia (P < 0.001).

CONCLUSIONS: Myosteatosis and sarcopenia, probably by reducing the handling of ammonia in the muscle, are independently associated to MHE and to the risk of overt HE in cirrhosis. In malnourished patients, the amelioration of nutritional status may be a possible goal to decrease both the prevalence of MHE and the incidence of overt HE.
The Modification of Quantity and Quality of Muscle Mass Improves the Cognitive Impairment After TIPS

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1Sapienza Università di Roma, Rome, Italy.

BACKGROUND: Hepatic encephalopathy (HE) is the major complication of transjugular intra-hepatic portosystemic shunt (TIPS). In cirrhotic patients, a correlation between sarcopenia and hepatic encephalopathy has been suggested.

AIM: to evaluate the evolution of the skeletal muscle quantity and quality at CT scan and of the patients’ cognitive impairment (both overt and minimal HE) before and after TIPS.

PATIENTS AND METHODS: 27 cirrhotic patients submitted to TIPS were studied. The modification of Skeletal Muscle Index (SMI), muscle attenuation, HE and plasma ammonia were evaluated before and after a mean follow-up of 9.8 ± 4 months after TIPS.

RESULTS: During the follow-up, the mean SMI and muscle attenuation increased significantly, although not uniformly in all patients. PHEs (Psychometric Hepatic Encephalopathy Score) and ammonia improved significantly in the patients with amelioration in SMI >10% (n = 16) and not in those without (n = 11) (PHEs: -1.6 ± 2 vs -4.8 ± 2.1; P = 0.0005; ammonia: 48.5 ± 28.7 vs 96 ± 31.5 µg/dl; P = 0.0004). Moreover, the prevalence of minimal HE (12.5% vs 73%, P < 0.001) as well as the number of episodes of overt HE during the follow-up were significantly reduced in the patients with improved SMI. MELD remained stable or worsened after TIPS and was not significantly different between the groups with or without SMI improvement.

CONCLUSION: The amelioration of muscle wasting and HE independent of liver function observed after TIPS supports the causal relationship between muscle wasting and HE.

Evaluation of Neurocognitive Function in Patients With Compensated and Decompensated Cirrhosis

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BACKGROUND: Cirrhosis is the end result of chronic liver damage caused by multiple entities. Up to 20%-60% of patients with cirrhosis are affected by a peculiar type of mild cognitive impairment related to selective attention and executive functions, visuomotor capacity, psychomotor speed, inhibition of response and selection of response that can only be detected by psychometry.

METHODS: An observational, cross-sectional, analytical study was carried out. A total sample of 126 patients was established, 64 patients for each group. The NeuroPsí instrument was applied to determine the domains (Orientation, Attention, Visual Episodic Memory, Verbal Episodic Memory, Language, Reading Writing, Executive Conceptual Functions and Executive Motor Functions); With the transcranial Doppler, the hemodynamic parameters such as velocity, pulsatility index, resistance index, as well as the apnea index to assess cerebral vasoreactivity were evaluated.

RESULTS: Up to now, 55 patients were studied, two groups were established: compensated cirrhotic 18 and decompensated, the gender ratio was 38% men and 62% women, with a median of 60 years. Compensated cirrhotics showed a higher percentage of patients without hepatic encephalopathy (HE) 65% vs 27.1%. The mean Child Pugh score was 7.47 ± 1.82. MELD Na mean for total patients was 12.98 ± 5.04. Of the masters, Reading Writing with 4.50 ± 0.89 for compensated and 4.85 ± 0.50 in decompensated (P = 0.07), in the domain of Executive Motor Functions with 5.69 ± 1.8 for compensated and 6.24 ± 0.89 decompensated (P = 0.16).

CONCLUSIONS: This study could not find significant differences in the averages obtained in the 8 cognitive domains explored, between the compensated and decompensated cirrhotic patients, nor correlation between the Child Pugh score and the performance in the cognitive tests; It is considered relevant to increase the sample of this study to have more solid evidence. In the cerebral hemody- namic parameters assessed by transcranial Doppler, there were no significant differences between compensated and decompensated patients.

Prevalence of cognitive impairment (minimal and overt HE) in the patients with or without improvement of SMI >10% at the end of follow-up

<table>
<thead>
<tr>
<th></th>
<th>SMI improvement&lt;10% (n=11)</th>
<th>SMI improvement&gt;10% (n=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal HE (PHEs&lt;4)</td>
<td>8/3 (72.7%)/ (27.3%)</td>
<td>2/14 (12.5%)/ (87.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>PHEs score</td>
<td>-4.8±2.1</td>
<td>-1.6 ±2</td>
<td>0.0005</td>
</tr>
<tr>
<td>Overt HE (yes/no)</td>
<td>9/2</td>
<td>10/6</td>
<td>0.3</td>
</tr>
<tr>
<td>OHE in the first 3 months (N of episodes/pt)</td>
<td>0.9±1.04</td>
<td>0.6±0.5</td>
<td>0.3</td>
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<tr>
<td>OHE in the following months (N of episodes/pt)</td>
<td>1.4±1.4</td>
<td>0.06±0.3</td>
<td>0.001</td>
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<tr>
<td>Venous plasma Ammonia (µg/dl)</td>
<td>96±31.5</td>
<td>48.5±28.7</td>
<td>0.0004</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>11.9±6.2</td>
<td>11.4±6.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Mean ± SD

[26]
Contributors to Balance Impairment in Adults With Cirrhosis and Hepatic Encephalopathy

Susan L. Murphy, ScD, OTR1, James K. Richardson, MD1, Jennifer A. Blackwood, PhD, PT, GCS, CEEAA2, Bawona A. Martinez, MA, OTR3, Emily J. Rayment, OTR4, Megan L. Park, MS, OTR5, Jeremy Louisant, MD6, Elliot B. Tapper, MD7

1University of Michigan, Ann Arbor, MI, USA; 2University of Michigan, Flint, MI, USA; 3Eastern Michigan University, Ypsilanti, MI, USA.

BACKGROUND: Falls are common and associated with significant morbidity for persons with cirrhosis and hepatic encephalopathy. In order to intervene with targeted rehabilitation efforts to reduce and prevent falls, a better understanding of mechanisms underlying balance deficits is needed. To this end, unipedal stance time (UST) is a useful measure of balance as it requires the integration of sensory, neurocognitive, and muscular factors.

METHODS: We prospectively enrolled 119 outpatients with cirrhosis and history of hepatic encephalopathy from the hepatology clinic at Michigan Medicine. The primary outcome was UST. Each patient was evaluated for demographic and clinical factors [Child Turcotte Pugh (CTP) class, MELD score], physical function (grip-strength and hip-strength using lateral plank time), neurocognitive factors [Numbers Connection Test (NCT) A and B, recognition reaction time accuracy - ability to catch or inhibit catching an instrumented stick under 'lights on' and 'lights off' conditions within 400 ms], and sensory factors (lower limb vibratory sensation and visual contrast). Falls self-efficacy, perceived ability to perform different tasks without falling, was also assessed. We evaluated bivariate Pearson correlations and developed a linear regression model to identify significant contributors to balance impairment.

RESULTS: Participants were 50% female, aged 62.9 ± 7.3 years, 80% CTP A, 18% CTP B, 2% CTP C, with MELD 11 ± 5. The mean UST was 12.7 ± 9.9 seconds (median = 9.42 seconds, IQR = 19.26). In bivariate analyses, UST was most highly correlated with lateral plank time (r = 0.61), followed by recognition reaction time accuracy [total, percent correct in lights on, and in lights off conditions (r = 0.47, r = 0.36, r = 0.33)] and NCT A and B tests (each r = 0.27). In multivariable regression, 54% of variance in UST was explained by significant factors of plank time, recognition reaction time accuracy, falls self-efficacy, age, and CTP. Based on standardized beta coefficients, plank time, CTP of B or C, and recognition reaction time accuracy were the strongest predictors. For every second increase of plank time, UST increases by 0.26 seconds on average. If classified by CTP of B or C, UST decreases by 5.8 seconds. For each additional percent correct on recognition reaction time accuracy, UST increases by 0.12 seconds.

CONCLUSIONS: The strongest factors associated with diminished balance, as indicated by UST, in this high fall-risk cirrhosis population are hip strength, clinical disease severity, and neurocognitive capacity. These findings support a rehabilitation approach that targets strengthening as well as neurocognitive training to address balance impairment.

Accuracy of DKI/DTI parameters for diagnosis of minimal hepatic encephalopathy among cirrhotic patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUROC</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<td>0.84</td>
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<td>0.73</td>
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</tr>
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<td>MK_CN</td>
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<td>0.78</td>
<td>0.71</td>
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<td>MK_Put</td>
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<td>0.86</td>
<td>0.80</td>
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<tr>
<td>MK_GP</td>
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<td>0.78</td>
<td>0.79</td>
<td>0.70</td>
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<td>MK_TH</td>
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<td>0.75</td>
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<td>0.80</td>
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<td>0.85</td>
</tr>
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<td>FA_Put</td>
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of Neuropsychological Status (RBANS), the Postoperative Encephalopathy Syndrome-Test and the Critical Flicker Frequency (CFF) assessment in regard to mortality in patients on the waiting list for liver transplantation.

**METHODS:** 143 patients awaiting liver transplantation were included. They underwent a test battery including the Inhibitory Control Test, the Repeatable Battery for the Assessment of Neuropsychological Status, the Postoperative Encephalopathy Syndrome-Test which provides the psychometric hepatic encephalopathy score (PHES) and the Critical Flicker Frequency assessment at study inclusion. The PHES was available for all patients (n = 143), the RBANS scores for n = 115, the ICT results for n = 99, and the CFF results for n = 136 patients. Basic characteristics (age, gender, underlying liver disease, accompanying diseases) and Model for End-stage Liver Disease (MELD)-Score at the time of study inclusion were documented. Follow-up was done for 5 years. Patients who either received a liver transplantation or dropped out of the study during the observation period were censored. The outcomes after HE in this contemporary Medicare-insured population experienced HE (26.4%). The median survival following cohort entry of those who did and did not develop HE was 5.78 and 3.4 years, respectively (P < 0.001). Multivariate analysis identified decreased survival with older age (HR 1.02, CI: 1.01–1.03), male sex (HR 1.21, CI: 1.19–1.24), ERSD (HR 1.08, CI: 1.01–1.14), and increasing Charlson Comorbidity Index (HR 1.2–1.42, CI: 1.17–1.48). Cirrhosis etiologies of HCV and alcohol were associated with improved survival (HR 0.87 CI: 0.85–0.90 and HR 0.88 CI: 0.85–0.90, respectively), while NAFLD was linked to increased mortality after HE (HR 1.03, CI: 1.01–1.06) and fewer 30-day readmissions (HR 0.37) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80) while NAFLD was linked to increased mortality after HE (HR 1.08, CI: 1.07–1.12). Hospital-days per person-year were 11.8 in patients with HE compared to 2.9 in those without (P < 0.001). Factors that were inversely associated with hospital utilization were Rifaximin use (HR 0.40, CI: 0.39–0.42) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80). Rifaximin use was associated with decreased hospital-days (HR 0.35, CI: 0.28–0.45) and fewer 30-day readmissions (HR 0.18, CI: 0.08–0.40), while gastroenterology consultation was associated only with a decreased risk of 30-day readmissions (HR 0.71, CI: 0.57–0.88) but not overall hospitalizations.

**CONCLUSIONS:** An abnormal PHES result is an indicator for an increased mortality risk, though less predictive than the MELD-Score.

**RESULTS:** Patients with abnormal PHES had a significantly higher mortality risk than patients with a normal PHES (P < 0.0001). Also patients with an abnormal RBANS result had a significantly higher risk to die than patients with a normal RBANS result (P = 0.038), but the difference was less significant compared to the PHES. Mortality risk did not significantly differ between patients with normal or abnormal CFF or ICT results. (CFF: P = 0.412, ICT: P = 0.202). In a binary logistic regression analysis the MELD-Score and diabetes were independent prognostic factors for mortality risk (MELD: P = 0.003; diabetes: P = 0.008). The MELD-Score turned out to have significant impact on the test results regarding the PHES (P < 0.0001), but not concerning the other tests (CFF: P = 0.903; RBANS: P = 0.065; ICT: P = 0.139).

**DISCUSSION:** The outcomes after HE in this contemporary Medicare-insured population are poor. The development of HE increases hospitalization utilization and worsens survival with few, potentially modifiable, targets for prospective study intervention.

**METHODS:** We examined data from a 20% random sample of US Medicare enrollees with cirrhosis and continuous Part D prescription coverage from 2008–2014. Those with a diagnosis of HE prior to or within 3 months after the diagnosis of cirrhosis was made were excluded. Incident HE was defined by ICD-9 code 572.2 and/or the initiation of a prescription for an HE-specific treatment (Neomycin, Lactulose, or Rifaximin). Outcomes included transplant-free survival and hospital-days or 30-day readmissions per person-year. Multivariate analysis was performed for survival (hazard ratios, HR, Cox regression) and hospital utilization (incidence rate ratios, IRR, negative binomial regression).

**RESULTS:** Among 186,160 Medicare-enrollees (median age 65 years) with cirrhosis, 49,164 experienced HE (26.4%). The median survival following cohort entry of those who did and did not develop HE was 5.78 and 3.4 years, respectively (P < 0.001). Multivariate analysis identified decreased survival with older age (HR 1.02, CI: 1.01–1.03), male sex (HR 1.21, CI: 1.19–1.24), ERSD (HR 1.08, CI: 1.01–1.14), and increasing Charlson Comorbidity Index (HR 1.2–1.42, CI: 1.17–1.48). Cirrhosis etiologies of HCV and alcohol were associated with improved survival (HR 0.87 CI: 0.85–0.90 and HR 0.88 CI: 0.85–0.90, respectively) while NAFLD was linked to increased mortality after HE (HR 1.08, CI: 1.07–1.12). Hospital-days per person-year were 11.8 in patients with HE compared to 2.9 in those without (P < 0.001). Factors that were inversely associated with hospital utilization were Rifaximin use (HR 0.40, CI: 0.39–0.42) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80). Rifaximin use was associated with decreased hospital-days (HR 0.35, CI: 0.28–0.45) and fewer 30-day readmissions (HR 0.18, CI: 0.08–0.40), while gastroenterology consultation was associated only with a decreased risk of 30-day readmissions (HR 0.71, CI: 0.57–0.88) but not overall hospitalizations.

**CONCLUSIONS:** The outcomes after HE in this contemporary Medicare-insured population are poor. The development of HE increases hospitalization utilization and worsens survival with few, potentially modifiable, targets for prospective study intervention.
BACKGROUND: Cirrhosis is associated with poor health related quality of life (HRQOL), cognitive and physical frailty (CF/PF), that manifest as covert/overt hepatic encephalopathy (CHE/OHE) and with incoordination and falls respectively. Tandem gait (TG; heel-toe) walking is a marker of PF. We aimed to determine the impact of LT on CF, abnormal TG, falls and HRQOL, in decompensated cirrhosis.

METHODS: We prospectively enrolled pts from the active LT wait list from 2011–2016. All pts underwent complete neurological examination, cognitive testing by the psychometric hepatic encephalopathy score (PHES), and HRQOL assessment using sickness impact profile (SIP, physical/psychosocial domains). All pts were followed up at 6 & 12 months post-LT at which point repeat testing was done. Cognitive frailty (prior OHE/CHE) & physical frailty (abnormal TD) and falls were analyzed pre/post-LT.

RESULTS: 61 pts completed all visits. The median (IQR) time to LT was 54 (16, 112.5) days. Majority were men (51, 84%), with HCV etiology (21, 34%). Pre-LT: Thirty (49%) had abnormal TD. Thirty (50%) had CHE. Thirty (49%) had prior OHE/CHE & 38 (62%) had prior CHE. Abnormal TD was signiﬁcantly more prevalent in pts with CHE than those without CHE. 37 (61%) had CHE, 20 (32.7%) with CHE & abnormal TD, 38 (62%) had prior OHE/CHE & 20 (32.7%) with OHE/CHE and abnormal TD. On multivariable analysis with abnormal TD as dependent variable physical SIP score [OR 1.12 (1.06–1.18) P = 0.024] and PHES [OR 1.25 (1.18–1.32); P = 0.007] compared to those with normal pre-LT TD. CONCLUSIONS: After LT, there is a sustained improvement in CF, abnormal TG and HRQOL from 6 through 12 months, which is accompanied by a lower rate of falls.

REFERENCES

P: 33 Junior Investigator

In Vivo Longitudinal 1H MRS Study of Hippocampal, Cerebral and Striatal Metabolic Changes in the Adult Brain Using an Animal Model of Chronic Hepatic Encephalopathy

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1Laboratory for Functional and Metabolic Imaging (LIFMET), Lausanne, Vaud, Switzerland; 2Center for Biomedical Imaging (CIBM), Lausanne, Vaud, Switzerland; 3École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Vaud, Switzerland; 4Service of Clinical Chemistry, University Hospital of Lausanne, Lausanne, Vaud, Switzerland; 5Swiss Center for Liver Disease in Children, Department of Pediatrics, University Hospitals Geneva, Geneva, Switzerland.

BACKGROUND: Chronic hepatic encephalopathy (CHE) is a severe complication of chronic liver disease (CLD) characterized by cognitive and motor deﬁcits. The diseased liver fails to metabolize toxins from the blood (ammonium, bilirubin etc.) which accumulate in the blood and brain.1 There is evidence that ammonium uptake rate differs among the brain regions.2 Since the CHE patients present various symptoms with different severity, the susceptibility to CHE and the mechanisms causing the damage may depend on the brain region. The aim of this study was to investigate, for the ﬁrst time, potential metabolic differences between hippocampus, cerebellum and striatum as key brain regions implicated in manifestation of CHE.

METHODS: Hippocampus (n = 7), cerebellum (n = 8) and striatum (n = 4) of adult male Wistar rats were scanned longitudinally using in-vivo 1H-MRS (SPECIAL sequence-TE = 2.8 ms, quantiﬁcation with LCMODEL) at 9.4T before (week 0) and after bile duct ligation (BDL-CHE model). Scans and blood tests were performed every two-weeks till week 8.

RESULTS: All BDL rats showed an increase in plasma bilirubin and blood ammonia validating the presence of CLD. Increase in brain Glutamine (Gln) was observed for all brain regions being the most pronounced in cerebellum (+134%-week 8) (Figure 1c). Furthermore, this increase showed a strong correlation with blood ammonia for all three brain regions (Figure 1b). The main brain organic osmolites (Inositol, Tauarine and total-Choline) displayed a similar decreasing trend in concentration as a response to Gln increase (osmoregulation) for both hippocampus and cerebellum, always having a stronger change for cerebellum. Interestingly, despite the smallest Gln increase, striatum showed more pronounced decrease in concentration of osmolites than hippocampus (Figure 1d). Also, trend towards a decrease in NAA and PE was observed uniquely for striatum (data not shown). A tendency of increase in Lactate was observed being the strongest for cerebellum (+84%-cerebellum, +8%-hippocampus, +5%- striatum) indicating a possible energy metabolism perturbation (Figure 1f). Brain regions displayed different antioxidant response with a decrease in Ascorbate being stronger in cerebellum (data not shown).

CONCLUSIONS: This is the ﬁrst study showing in-vivo longitudinal analysis of neurometabolism in three different brain regions in a model of CHE. Hippocampus and cerebellum displayed similar trends in metabolite changes during the course of disease, while the changes were much more pronounced in cerebellum. Striatum showed differences in metabolic response when compared to the other brain regions. Clinical relevance of these ﬁndings remain to be determined. We conclude that different brain regions are differentially susceptible to the metabolic consequences of CLD, a ﬁeld which warrants further study.

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Hepatic Encephalopathy Is an Independent Risk Factor for the Occurrence of Infection in Cirrhotic Patients With Acute Decompensation

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BACKGROUND: Hepatic encephalopathy (HE) in cirrhotic patients increases mortality with worsening of HE grade 1. Infection is important in the pathogenesis and a common reason for progression to HE and death in these patients 2. However, HE role as a predisposing factor to infection in patients with acute decompensation (AD) is not known. It’s recently shown that CNS injury leads to secondary immunodeﬁciency, and signiﬁcantly increases susceptibility to infection (Pneumonia is the commonest serious complication with stroke 3), with development of the so known CNS injury-induced immunodepression (CIDS). But those studies focused only on organic brain injuries, like stroke, TBI and SCI. Our study aims to determine whether HE is associated with the development of new infections in cirrhotic patients with AD.

Table 1: The Table shows results of comparisons of bacterial spore scores in patients with and without HE. The HE group had significantly higher bacterial spore scores compared to the non-HE group. The HE group also had a higher total bacterial spore score compared to the non-HE group. The HE group also had a higher total bacterial spore score compared to the non-HE group. The HE group also had a higher total bacterial spore score compared to the non-HE group. The HE group also had a higher total bacterial spore score compared to the non-HE group. The HE group also had a higher total bacterial spore score compared to the non-HE group.

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WITHDRAWN
METHODS: Patients were identified at two institutions (ADAMS & UCL) as part of ongoing prospective studies of AD. Culture positive infections and severity of HE (classified by West Haven Criteria) were measured on the day of admission, and new culture positive infections were assessed for up to 28 days after admission. Organ failures were defined as CLIF-organ failure score. Categorical and continuous variables were compared using chi square analysis and one-way ANOVA respectively. "Where appropriate", differences in infection rates were assessed using Cox regression models. The results of this study show for the first time that, in AD patients, overt HE not only associated with higher mortality but is also an independent risk factor for infection. We also showed that Age and Circulatory failure are independent risk factors for infections. That would make them, after further studies, an indication for prophylactic antibiotics.

CONCLUSIONS: The results of this study show that rifaximin at the recommended human dose may help reduce brain Gln levels in early stages of HE. These findings raised the question of the efficacy of the dose used at later stages. Therefore we hypothesized that the effect of rifaximin on neurometabolic profile may be dose-related. In this study, the effects of a dose 6.2x that recommended in humans 2 were assessed in vivo and longitudinally in BDL rats. They were compared with non-treated rats (n = 17) and human-dose treated rats (15.7 mg/kg/day, n = 12).

METHODS: Plasma measurements of NH4+, bilirubin and 1H-MRS scans were performed on adult Wistar rats (n = 8) before BDL (‘week 0’) and at weeks 2, 4, 6, 8 post-BDL. Rifaximin was administered twice daily (6x-human-dose c = 97.3 mg/kg/day) starting two weeks after BDL-surgery (‘week 2’). In vivo 1H-MRS was performed on a 9.4 Tesla MRI system. Changes in metabolites were studied in the hippocampus (2 × 2.8 × 2 mm3) using SPECIAL2 sequence (TE = 2.8 ms). Metabolite concentrations were estimated by LCModel using water as internal reference. Open field test was performed at week 4, 6 and 8 to evaluate motor activity.

RESULTS: Plasma measurements of bilirubin confirmed the presence of CLD in all groups of rats. They displayed similar ammonium concentration across groups (Figure 1a). 1H-MRS revealed some differences between the groups were observed in behavioural tests, but the high-dose rifaximin group at week 6 and at week 8, both in absolute value and relative to week 2 (+42% vs +118% at week 8, Figure 1b). Moreover, a decrease of glutamine was observed between week 4 and week 6 in the high-dose rifaximin group (–10%), contrary to the non-treated group (Figure 1b). Also, in the high-dose rifaximin group, decreases in the following metabolites were less pronounced during the time course of the study: myo-inositol, taurine, glutamate, ascorbate, creatinine, total creatine (Figure 1c).

CONCLUSIONS: While rifaximin at human dose appeared to have an effect only at the early stages of the disease, a higher dose gave stronger positive effects on the neurometabolic profile. Importantly, no differences between the groups were observed in behavioural tests, but the high-dose rifaximin rats had the tendency to move less. It is therefore possible that such a high dose of antibiotics also leads to some undesirable side-effects such as electrolyte abnormalities or inherent drug toxicity.

REFERENCES
Probiotics Combined With Rifaximin for the Treatment of Chronic Hepatic Encephalopathy: A Longitudinal In Vivo 1H-MRS Study of Brain Metabolism Using BDL Rats

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BACKGROUND: Chronic hepatic encephalopathy (HE) is a severe complication of chronic liver disease (CLD), and finding the right treatment to reduce HE episodes before liver transplant remains a challenge. Both rifaximin (non-abSORbable antibiotic) and probiotics are currently used to reduce HE symptoms, but their precise effect on brain metabolites has never been studied. Our aims were: 1) to assess in vivo and longitudinally the effect of the combination of probiotics and rifaximin on bile duct ligated (BDL) rats in different brain regions; and 2) to compare these results with both non-treated (n = 17) and rifaximin-only treated rats (n = 12).

METHODS: In vivo 1H-MRS at 9.4 Tesla combined with biochemical tests (plasma NH4, bilirubin) and microbiota analysis were performed on adult Wistar rats (n = 9) before BDL3,4 (week 0) and at weeks 2, 4, 6 and 8 after surgery. Evolution of metabolites was studied using the SPECIAL sequence (TE = 2.8 ms) in the hippocampus (2 × 2.8 × 2 mm3) and cerebellum (2.5 × 2.5 × 2.5 mm3). Metabolite concentrations were estimated using LCModel and water as internal reference.

RESULTS: All rats displayed the characteristic rise in plasma bilirubin, regardless of treatment group, as well as a similar ammonium increase (Figure 1a). The characteristic pattern of chronic HE was observed (Figure 1c): a gradual increase of brain glutamine followed by a gradual decrease in the other brain osmolytes (myo-inositol, taurine, total choline) and a later decrease of glutamate and creatine (~4% vs ~16%). In the hippocampus, rats receiving both probiotics and rifaximin exhibited a smaller increase in brain glutamate even at week 8 after BDL compared to non-treated rats (~99% vs ~136%, Figure 1d) and a smaller decrease in brain myo-inositol and glutamate (~20% vs ~30% and ~7% vs ~13%, respectively). Also, bifidobacteria concentration was slightly higher in the ‘probiotics + rifaximin’ group at week 8 (Figure 1b). Finally, the administration of rifaximin associated with this probiotic showed more beneficial effects than rifaximin only, and both could be used to maintain a balanced microbiota and may provide opportunities for reducing the spread of antibiotic resistances.

CONCLUSIONS: To conclude, some promising changes were induced in the neurometabolic profile of BDL-rats who were treated with this specific probiotic and rifaximin (glutamine, myo-inositol, creatine and glutamate).

REFERENCES:
CONCLUSION: Rifaximin prescribed for HE in patients listed for liver transplantation improved outcomes on the waiting list with a significant reduction in admissions related to spontaneous bacterial peritonitis, ascites and AVB and indicating potential beneficial impacts of rifaximin beyond HE in ACLD.

Background: Lipopolysaccharide (LPS) and ammonia act synergistically in mediating the severity of hepatic encephalopathy (HE) in cirrhosis. Although LPS results in neuroinflammation, it is not clear whether it induces hyperammonemia (HA) contributing to HE. This study addressed the following questions: 1) Does LPS worsen HA in cirrhosis? 2) Does treatment with an antagonist (TAK242) of the LPS receptor, toll-like receptor 4 (TLR4), prevent HA? 3) Is a TLR4 knock-out (TLR4-/-) animal protected from HA? If so, what is the underlying mechanism? Do they have a more effective urea cycle?

Methods: Study 1: Sprague Dawley rats were treated with LPS (0.025 mg/kg, ip.) 4 weeks after bile duct ligation (BDL). 4 groups of rats were studied: sham (n=4), BDL (n=4), BDL+LPS (n=6) and BDL+TAK242 (10 mg/kg ip.) 3 hours before LPS injection (n=7). Study 2: 4 groups of mice were studied: wild type control (WTC, n=7), WT with HA (WTH, n=10), TLR4-/- control (TLR4-/-C, n=10) and TLR4-/- with HA (TLR4-/-H, n=10). HA was induced by adding 0.28M ammonium chloride to drinking water for 3 days. For both studies, plasma ammonia and liver gene expression (qPCR, data shown as 2^-DDCT compared to sham/WT) of the 5 urea cycle enzymes (UCEs) were assessed. For study 2, protein expression of the key, rate-limiting enzyme carbamoyl phosphate synthetase 1 (CPS1) was also assessed (Western Blot, immunohistochemistry).

Results: Study 1: There was a stepwise increase in plasma ammonia throughout sham, BDL and BDL+LPS groups (P < 0.001). Pre-treatment with TAK242 prior to LPS injection in BDL rats was
associated with a reduction in plasma ammonia (P < 0.01, Figure 1a) and a higher coma-free survival rate (100% vs. 15%). Gene expression of all UCEs showed a stepwise decrease throughout sham, BDL and BDL+LPS (all P < 0.05), which was prevented by TAK242 (all P < 0.05). This was most pronounced for CPS1, for which expression levels in the TAK242-treated group were restored to that of the sham animals (Figure 1b). Study 2: In TLR4-/- mice, the increase in plasma ammonia was less compared to WT mice (P = 0.001). Although no significant changes were found for gene expression of UCEs between groups, protein expression of CPS1 was significantly higher in TLR4-/- mice as compared to WT mice, as shown by both Western Blot and immunohistochemistry.

CONCLUSIONS: These data suggest that TLR4 signaling contributes to the development of hyperammonemia by modulating the urea cycle function. Inhibition of TLR4 with TAK242 offers a potential novel therapy for HA and HE in cirrhosis.

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Potassium Deficiency Compromises Urea Synthesis and Markedly Increases Ammonia in Rats
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BACKGROUND: Potassium deficiency decreases gene expression, synthesis of proteins, and growth in plants, bacteria, rodents and humans.1–4 The effect of hypokalemia on liver protein synthesis is scarcely described. Early studies have established an association between hypokalemia and development of hepatic encephalopathy in chronic liver disease.5–6 We investigated the effects of potassium deficiency on synthesis of liver proteins including urea cycle enzymes and the regulation of urea synthesis in rats.

METHODS: Female Wistar rats were fed a K+-free diet for 13 days. Half of the rats were then repleted with K+ for one week following depletion. K+-depleted and -repleted rats were compared to free-fed and pair-fed controls. We examined the urea cycle enzyme mRNAs and proteins in liver tissue, the in vivo Capacity of Urea-Nitrogen Synthesis (CUNS) and plasma ammonia concentrations. Also, we measured hepatic albumin gene and protein expression, and potassium levels in plasma, liver, kidney and muscle tissues.

RESULTS: The diet induced hypokalemia of 1.9 ± 0.4 mmol/L compared to pair-fed controls (3.6 ± 0.2 mmol/L). Muscle and kidney tissue potassium concentrations were decreased, whereas protein expressions of albumin, the urea cycle enzymes, and glutamine synthetase in liver tissue were normal. CUNS was reduced by 33%. Plasma ammonia concentrations were eight-fold elevated to 235 (95% CI: 194–287) μmol/L compared to pair-fed controls 29 (95% CI: 26–32) μmol/L. Repletion of potassium normalized the changes.

CONCLUSIONS: Hypokalemia markedly increased plasma ammonia concentrations. The capacity for urea synthesis was impaired, but only moderately so, and further studies are needed to fully explain the causes of hyperammonemia.

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Precipitants of Hepatic Encephalopathy, In-hospital Mortality and Its Predictors
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BACKGROUND: Hepatic encephalopathy (HE) is a common complication of liver dysfunction, including acute liver failure and liver cirrhosis. HE presents as a spectrum of neuropsychiatric symptoms ranging from subtle fluctuating cognitive impairment to coma. It is a significant contributor of mortality in patients with liver disease. Common culprits include gastrointestinal bleeding, infection, constipation, hypokalemia, hyponatremia, and medications such as opiates and benzodiazepines. This study aims to evaluate the change in common precipitants of HE, in-hospital mortality and its predictors.

METHODS: This descriptive study was conducted in Hepatology division of Asian Institute of Medical Sciences, Hyderabad, Pakistan from October 2018 to April 2019. A total of 82 cirrhotic patients with HE were included in the study. Frequency of precipitating factors were determined and in-hospital mortality was evaluated.

RESULTS: A total of 82 cirrhotic patients with mean age 52.31 years, with males 62.2%. Common etiology for cirrhosis was HCV 64.63%, 56.09% were CTP B, 36.58% patients had MELD in between 11–15. According to West Haven criteria most common grades were Grade II 52.43%, Grade III 17% and Grade IV 16%. Most common precipitants were hyponatremia 18%, constipation 12%, hypokalemia 5%, infections 10%, variceal upper GI bleeding 4%, 24% had mixed precipitants and in 27%
patients no precipitant found. 42.7% had Acute Kidney Injury (AKI) mostly associated with electrolyte imbalance. 70.7% were improved and discharged, 11% were expired, 18.3% discharged on request. AKI, SBP and Shock were associated with high mortality.

CONCLUSIONS: Electrolyte imbalance, constipation and infections were leading causes of HE. AKI was independent predictor of HE and in-hospital mortality along with SBP and shock.

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To Assess Frequency of Hepatic Encephalopathy in Spontaneous Bacterial Peritonitis Patients

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BACKGROUND: Hepatic encephalopathy (HE) is a commonly encountered complication in cirrhosis. The incidence of HE ranges from 2% to 20% per year in patients with liver cirrhosis. HE is associated with increased morbidity and mortality as well as significant utilization of health care resources. Most cases of signifiant HE are generated by gastrointestinal bleeding, infection, concomitance, electrolyte imbalance and medications. Spontaneous bacterial peritonitis (SBP) is an independent predictor of HE. We evaluated frequency of HE in SBP patients.

METHODS: This cross-sectional study was conducted at the Gastro-hepatology section of Asian Institute of Medical Sciences in Hyderabad, Pakistan from April 2017 to March 2019. 120 Patients with paracentesis-proven SBP (Absolute Neutrophils counts (ANC) >250/mm3), aged from 18 to 80 years were included. Frequency of HE evaluated.

RESULTS: A total of 120 patients of SBP with mean age 47.80 years, with 88 (73.3%) males and 32 (26.7%) females were examined. Most common causes were HCV (61.7%), 23 were CFP (17.5%) and 99 were Child C (82.5%). HE was present in 75 (62.5%) with most common grades were II (29.33%) and III (29.33%) and IV (21.33%). Mean ANC 5086, 96 (80%) were PPI users and 64.58% have HE.

CONCLUSIONS: Hepatic encephalopathy has strong association with SBP and PPI use. Screening for and treatment of HE in all patients with SBP should be considered and over-the-counter PPI use should be restrained.

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A Sensitive and Convenient Protocol for Determining Brain Water Content in Rats using a Moisture Analyzer

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BACKGROUND: Brain water content represents a major endpoint in studies of hepatic encephalopathy and the control patients without any neurological disease.

METHODS: Female Sprague-Dawley rats (248 ± 41 g bw) undergoing a 3-hour protocol for acute hyponatremia were studied. Frontal cortex was pulverized frozen with a metal mortar, and the frozen powder was placed in a moisture analyzer (a Moisture Analyzer P: 43 Junior Investigator Copyright © 2019 by The American College of Gastroenterology. Unauthorized reproduction of this article is prohibited.
CONCLUSIONS: In this retrospective study, arterial ammonia at the time of listing for liver transplanted patients, ammonia levels correlated with the presence of post-op complications (independent predictor of the presence of acute-on-chronic liver failure (ACLF) (ammonia measured at the time of assessment for transplant. All patients were closely followed up until death A retrospective observational study of 300 sequential cirrhotic adult patients listed for liver transplantation between January 2015 and December 2018 was undertaken. All patients had an arterial ammonia measured at the time of assessment for transplant. All patients were closely followed up until death or transplantation. The main outcomes were hospital admissions (and number of organ failures), infection and mortality. Chronic Liver Failure-Sequential Organ Failure Assessment criteria were used to determine the presence of organ failures. For the transplanted patients, post-op complications were recorded.

RESULTS: 200 (66.7%) were male with mean age of 54.29 ± 10.4. Mean follow-up time was 722.6 days. 266 (88.7%) patients were transplanted, 15 (5.0%) were de-listed for being too sick for transplant or following clinical improvement, 14 (4.7%) died on the list and 3 (1.0%) were alive on list 97 (32.3%) patients were hospitalized on the waiting list and 60 (20%) had evidence of at least one infection. On multivariate analysis, ammonia correlated with hospitalization (P = 0.001), infection (P = 0.001) and all-cause mortality (P = 0.001). Of the patients that had at least one hospital admission, ammonia was an independent predictor of the presence of acute-on-chronic liver failure (ACLF) (P = 0.01811). For the transplanted patients, ammonia levels correlated with the presence of post-op complications (P < 0.001).

CONCLUSIONS: In this retrospective study, arterial ammonia at the time of listing for liver transplantation was an independent predictor of hospitalization, ACLF, infection and mortality. These data suggest that blood ammonia may be an important determinant of wait-list survival and further prospective studies are warranted.

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Risk of Recurrent Hepatic Encephalopathy (HE) in Patients With Liver Cirrhosis: A German Registry Study
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BACKGROUND: Patients with Hepatic Encephalopathy (HE) show a low quality of life, recurrent hospitalizations and an increased mortality. We aimed to assess the natural course of patients after a recent HE-episode under the conditions of the German health system, as respective data were not available.

METHODS: Fifteen sites from Germany - 8 of them liver transplant (LT) centers - took part in an observational prospective study including cirrhotic patients who had been hospitalized due to an acute episode of HE within 3 months before recruitment. Age < 18 years, no liver cirrhosis, malignancies and current hospitalization were exclusion criteria. Demographic and clinical data, health related quality of life (HRQoL) score SF-36, psychometric hepatic encephalopathy score (PHES) and critical flicker frequency (CFF) were assessed and monitored quarterly for one year. Primary endpoint was a novel clinical manifestation of HE necessitating hospital admission. Secondary endpoints were the combined endpoint of hospital admission for a novel HE episode and/or death, the dynamics of the West Haven Criteria (WHC) as well as changes in CFF, PHES and SF-36.

RESULTS: A total of 115 patients were recruited. Forty-four patients (12.4%) died during the study period due to complications of liver cirrhosis other than HE. For 67 subjects follow-up data were available in accordance with the protocol. After a median of 113 days half of the per protocol cohort (N = 34) was re-admitted due to a recurrent manifestation of HE. The patient groups with and without re-hospitalization differed significantly regarding recruitment sites (LT centers vs no LT centers) (P = 0.005), interval from discharge to recruitment (P = 0.007), history of more than 4 HE relapses prior to recruitment (P = 0.029), SF-36 mental score (P = 0.046) and PHES ≤ −3 (P = 0.004), whereas CFF, clinical (e.g. MELD score, WHC grade) and laboratory data did not differ. Of note, CFF performance was correct only in about half of both, the total and the per protocol group. Patients with incorrect CFF performance had worse PHES results than those with valid CFF measurement. Multiple logistic regression analysis revealed a PHES test result of ≤ −3 as an independent risk factor for re-hospitalization (P = 0.046).

CONCLUSIONS: Mortality in our cohort is comparatively low. Despite advanced treatment strategies, patients with a history of HE are still sincerely jeopardized to develop recurrent clinical HE. The PHES test appears useful for detection, monitoring and stratification of recurrent HE. Patients with PHES ≤ −3 at baseline had an increased risk of deterioration.

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Nonselective Beta-blocker Use is Associated With Increased Hepatic Encephalopathy-Related Readmissions in Patients With Cirrhosis
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BACKGROUND: Hepatic Encephalopathy (HE) is a reversible syndrome of impaired brain function that is associated with frequent hospitalizations and decreased survival in cirrhotic patients. Nonselective
beta-blockers (NSBB) are the mainstay of pharmacologic treatment for portal hypertension and prevention of variceal bleeding. Due to their effects on hepatic blood flow, we hypothesized that NSBB use would decrease portal flow, leading to increased HE-related hospitalizations independent of liver disease severity. This study was done to assess the effect of NSBB use on HE-related readmissions.

METHODS: We examined all the patients with cirrhosis admitted at Baylor University Medical Center between January 2013 and July 2018. The outcome measure of HE-related readmissions was analyzed in patients taking NSBB vs. patients not taking NSBB using Cox proportional hazards regression model. The model was adjusted for age, sex, Model for End-Stage Liver Disease (MELD) score, selective beta-blocker (SBB) use, ascites, and history of esophageal varices (EV) and transjugular intrahepatic portosystemic shunt (TIPS). The Kaplan-Meier method and log-rank test were used to compare the cumulative incidence of HE-related readmissions between the aforementioned groups.

RESULTS: There were 393 patients in this study with a mean age of 58.1 ± 10.2 years and a male predominance. The mean MELD score was 19.6 ± 7.7. The median time between the first admission and future readmission was 1.9 months with interquartile range of 4.8 months. The cumulative incidence of HE-related readmissions was significantly higher in patients taking NSBB compared with patients who were never prescribed NSBB (P < 0.001) (Figure 1). This effect was not seen for patients who were taking SBBs. In multivariate analysis, after adjusting for age, sex, MELD score, SBB use, ascites, history of EV and TIPS, NSBB use was independently associated with increased risk of HE-related re-hospitalizations; Hazard ratio was 2.82 (95% confidence interval: 1.81–4.41).

CONCLUSIONS: NSBB use is independently associated with increased HE-related readmissions in patients with cirrhosis, regardless of liver disease severity. Thus, NSBBs should be used cautiously in patients who have experienced a prior HE episode. However, further prospective studies are needed to determine the impact of NSBB on portal hypertension complications.

Driving Simulation During Functional MRI Scanning Shows Distinct Neural Activation Patterns in Patients With Cirrhosis Using Human Connectome Project Guidelines

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BACKGROUND: Cirrhosis-related cognitive dysfunction can result in car crashes due to impaired navigation skills & slowed reaction times. There is insufficient understanding of the neural basis of this impairment.

AIM: Determine feasibility of using an MRI-compatible functional MRI (fMRI) driving simulator and differences in performance of cirrhotics vs controls.

METHODS: We recruited cirrhotic outpatients and controls between ages 25–70 years, were current drivers, were candidates for MBI & free of alcohol/drug use. Cirrhosis did not have active HE. All subjects underwent an fMRI-compatible task consisting of simulated driving on a single lane highway. The simulation presented 4 blocks of 4 scenarios (1) straight section (SS) (2) Curved highway without oncoming traffic in the opposite lane (No Traffic) (3) Curved highway with oncoming traffic in the opposite lane (Traffic) and (4) Curved highway with oncoming traffic while responding to a ringing cellphone (Traffic + Distractor). Figure 1a,b. Contrast images between curated sections were created. SS was used as a baseline.

Group-analysis was performed for each group using these three contrasts via human connectome project guidelines.

RESULTS: Seven cirrhotic patients [MELD 7 (6, 11), 4 HCV, 2 Alcohol 1 NASH] and five controls completed the study. Controls & cirrhotics had statistically similar age 60 ± 15.5 vs 61.8 ± 10, P = 0.08, and gender (men 50% vs 20%, P = 0.3). Patients and controls had similar driving duration of driving 44 (42, 50) vs 45 (24, 51), P = 0.48. On MRI driving simulation: Mean activations: As the driving task complexity increased from No-traffic to Traffic to Traffic + Distractor states, we observed a shift of increased activation from parietal (precuneus, supramarginal and angular gyrus) and visual (lingual gyrus, V1 and V2) to frontal (dorsolateral prefrontal cortex, anterior cingulate cortex), and sub-lobar regions (caudate, putamen, pallidum, insula, and thalamus). This pattern reveals a gradual shift from basic visuo-spatial to complex performance brain regions regardless of control or cirrhosis group. Between-group activations: During both Traffic and Traffic + Distractor conditions, cirrhotic patients showed significantly lower activation than controls in brain regions associated with top-down attentional processing (posterior cingulate cortex), error detection and conflict monitoring (anterior cingulate cortex), attentional resource allocation (paracingulate gyrus), visual attention regulation (superior parietal lobule), inhibitory control (left middle frontal gyrus) and regions associated with regulation of voluntary movement (left pallidum, putamen) (Figure 1c).

CONCLUSIONS: Using MRI-compatible driving simulation, patients with cirrhosis demonstrated suppressed attention regulation circuits and sensorimotor control compared to controls, which worsened when distractors such as cellphone use were included. This is likely the neural basis for impaired driving skills in cirrhosis.

Developing a New Animal Model of Episodic Hepatic Encephalopathy

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BACKGROUND: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome, a major complication of chronic liver disease (CLD)/cirrhosis. The primary cause of hospital admissions for cirrhotic patients is an overt episode of HE. Precipitating factors of HE frequently lead to an increase in blood ammonia. Patients who have experienced multiple episodes of HE are associated with persisting neurological complications post-liver transplantation. Currently, the impact of HE episodes on neurological integrity is unknown. We hypothesize that multiple episodes of HE will accelerate and/or intensify neurological deterioration. To date, an animal model of episodic HE is lacking. Therefore, our goal was to characterize an animal model of episodic HE (precipitated with ammonia) and to evaluate the impact of cumulative episodes on neurological status in cirrhotic rats.

METHODS: Animal model of CLD and HE: 6-week bile duct-ligation (BDL) rats, and Sham-operated controls were used. BDL and Sham rats were divided in two groups, episodic and non-episodic. Injection (ip) of ammonium acetate was used to induce episodes of overt HE (pre-coma, loss of righting reflex) every 4 days starting 3 weeks post-BDL surgery (total 5 episodes). Additives were injected as vehicle for non-episodic groups. Two days following the last HE episode, we assessed motor-coordination (Rotarod), anxiety (elevated plus maze, EPMST), as well as short-term and long-term memory (novel object recognition) in all groups. Upon sacrifice, plasma ammonia was measured.

RESULTS: The concentration of ammonia required to induce an episode of overt HE in BDL rats lessened with each subsequent episode, ranging from 7 to 4.5 mmol/kg. Short-term memory (P < 0.05) and motor-coordination (P < 0.05) were impaired in both non-episodic and episodic BDL groups compared to respective Sham-operated controls. Long-term memory impairment (P = 0.06) and increased anxiety (P = 0.06, P = 0.05) were exclusively found in episodic BDL rats compared to non-episodic BDL rats. Moreover, there was an increase in blood ammonia (≥ 30.4%), P = 0.06 in episodic compared to non-episodic BDL rats, suggesting that although episodic-BDL rats recover from each HE episode, baseline (pre-episode) ammonia remain higher than non-episodic BDL rats.

CONCLUSIONS: Cumulative HE episodes escalate neurological impairments in cirrhotic-BDL rats. Thus, this new episodic HE model represents a good approach to explore the pathological mechanism arising from multiple episodes, as well as further investigate whether higher hyperammonemia and/or increased brain sensitivity to ammonia is responsible for more complex neurological manifestations in episodic HE, BDL rats. Moreover, this model is an excellent platform to investigate novel therapies to prevent/treat episodic HE.

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Aminoglycosides and Metronidazole for the Prevention and Treatment of Hepatic Encephalopathy in Adults With Cirrhosis

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BACKGROUND: The EASL/ASALD guidelines stipulate that both neomycin and metronidazole may be used as alternatives for the treatment of overt HE, whereas the Italian guidelines state that these antibiotics are currently not recommended, mainly because of their potential systemic toxicity. This study aims to evaluate the impact of aminoglycosides and metronidazole vs. placebo, non-absorbable disaccharides (NAD) and other active treatment, for the management of HE in adults with cirrhosis.

METHODS: Animal model of CLD and HE: 6-week bile duct-ligation (BDL) rats, and Sham-operated controls were used. BDL and Sham rats were divided in two groups, episodic and non-episodic. Injection (ip) of ammonium acetate was used to induce episodes of overt HE (pre-coma, loss of righting reflex) every 4 days starting 3 weeks post-BDL surgery (total 5 episodes). Additives were injected as vehicle for non-episodic groups. Two days following the last HE episode, we assessed motor-coordination (Rotarod), anxiety (elevated plus maze, EPMST), as well as short-term and long-term memory (novel object recognition) in all groups. Upon sacrifice, plasma ammonia was measured.

RESULTS: The concentration of ammonia required to induce an episode of overt HE in BDL rats lessened with each subsequent episode, ranging from 7 to 4.5 mmol/kg. Short-term memory (P < 0.05) and motor-coordination (P < 0.05) were impaired in both non-episodic and episodic BDL groups compared to respective Sham-operated controls. Long-term memory impairment (P = 0.06) and increased anxiety (P = 0.06, P = 0.05) were exclusively found in episodic BDL rats compared to non-episodic BDL rats. Moreover, there was an increase in blood ammonia (≥ 30.4%), P = 0.06 in episodic compared to non-episodic BDL rats, suggesting that although episodic-BDL rats recover from each HE episode, baseline (pre-episode) ammonia remain higher than non-episodic BDL rats.

CONCLUSIONS: Cumulative HE episodes escalate neurological impairments in cirrhotic-BDL rats. Thus, this new episodic HE model represents a good approach to explore the pathological mechanism arising from multiple episodes, as well as further investigate whether higher hyperammonemia and/or increased brain sensitivity to ammonia is responsible for more complex neurological manifestations in episodic HE, BDL rats. Moreover, this model is an excellent platform to investigate novel therapies to prevent/treat episodic HE.

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Extent of Sarcopenia Does Not Correlate With Degree of Minimal Hepatic Encephalopathy in Patients on Treatment for Hepatic Encephalopathy

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BACKGROUND: Minimal hepatic encephalopathy affects over half of the patients with cirrhosis. It leads to deterioration of quality of life due to cognitive deficit. Both presence of sarcopenia and portosystemic shunts have been implicated in development of minimal hepatic encephalopathy. We retrospectively assessed the significance of sarcopenia and presence of portosystemic shunts in patients with minimal hepatic encephalopathy. METHODS: Patients with cirrhosis of liver attending the liver clinic at University of Padua underwent a detailed elective outpatient assessment for neurocognitive function. This included Psychometric Hepatic Encephalopathy Score (PHES), computer based tests, and EEG. We then selected patients who underwent a computed tomography for any reasons within 3 months of the neurocognitive assessment. The degree of sarcopenia and presence of portosystemic shunts was evaluated on the scan. Presence of more than one shunt was accounted and adjusted for appropriately using a physiological approach previously described.

RESULTS: A total of 120 patients had a CT scan within 3 months of the neurocognitive assessment. Of these, 100 were found to be suitable for analysis. Mean age of the patients was 59 ± 9.7 years and 73% were males. Median Child Pugh score was 8 (Q1 6–10) and MELD was 12 (Q1 10–18). Alcohol and viral etiologies responsible for 40% and 39% cases respectively. Based on Psychometric Hepatic Encephalopathy Score (PHES), 39% had minimal hepatic encephalopathy. Medication details were available for 87 patients, 70% of whom were on some form of treatment of hepatic encephalopathy with lactulose, antibiotics, or probiotics. The degree of cognitive dysfunction (PHES) correlated significantly with education (r = 0.33), shunt size (r = 0.45), and degree of hyperammonemia (r = 0.48), but not with sarcopenia or degree of hepatic dysfunction. Correlation between total effective shunt size and PHES was more pronounced in women (r = 0.48). Upon multivariate analysis, none of these variables predicted PHES. EEG mean dominant frequency correlated significantly with total effective shunt size (r = 0.30), ammonia (r = 0.34), and Child-Pugh score (r = 0.38). None of the parameters significantly correlated with critical flicker frequency. There was no difference in the degree of sarcopenia among patients with and without MHE or history of overt HE. Moreover, degree of sarcopenia did not correlate with PHES, critical flicker frequency, ammonia level, or Child-Pugh score. Effective size of portosystemic shunt was higher in patients with MHE. CONCLUSIONS: Among patients with cirrhosis on anti-encephalopathy treatment, presence of sarcopenia does not correlate with neurocognitive parameters. Presence of large portosystemic shunts correlated with neurocognitive impairment.

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Diagnosis of Covert Hepatic Encephalopathy Is Influenced By Multiple Non-cognitive Variables That Varies by Testing Strategy

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BACKGROUND: Covert hepatic encephalopathy (CHE) is a serious complication of cirrhosis that manifests as an amnestic cognitive dysfunction. Diagnosis is based on examining cognitive functions, but results are influenced by multiple non-cognitive factors such as sleep and medications but data regarding the influence of other non-cognitive covariates is limited. We aimed to examine the potential non-cognitive variables that could influence testing on the psychometric hepatic encephalopathy score (PHES) and the encephalopathy stroop.

METHODS: Patients between ages 20-75 years were enrolled from clinic between 2012–2018. Those with severe uncontrolled psychiatric comorbidities were excluded as were those actively abusing alcohol or drugs. All patients underwent testing for CHE based on 2 testing strategy as recommended by the AASLD/EASL guidelines. Demographics and details of comorbidities were collected. CHE was diagnosed based on published norms. Appropriate t tests and logistic regression were done. Dependent variable was CHE on PHES and Stroop.

RESULTS: We enrolled a total of 257 patients with mean age 61.1 ± 8.3, 72% were males, HCV was the predominant etiology 96 (37.3%). Median BMI was 29 (26, 34). Median education was 13 (12, 16) years. Median MELD was 11 (7.25, 15) with median child’s score of 6 (5, 8). Charlson comorbidity score (CCI) was 5 (4, 6). Eighty-five (33%) had a history of prior OHE and were on lactulose (13), rifaximin (9) or both (63), 95 (37%) had ascites with 58 (61%) controlled on diuretics and 17 (18%) had a history of SBP. 41 (16%) had a history of variceal bleeding. In terms of comorbidities 34.2% had Diabetes Mellitus, 58% had Hypertension, 11% had Coronary artery disease, 14% had hyperthyroidism, 2% had CHE, 2.3% had COPD, 30% had depression and 87% were controlled on medications. 2.3% had post traumatic stress disorder (PTSD) and were on medications. 14% were on chronic narcotic medications. On cognitive testing 109 (42.4%) had CHE with a median PHES score of 3 (~7, 0) whereas 206 (80%) tested positive on encephalopathy stroop. On univariable analysis hypertension was found to be significant only for stroop. On multivariable analysis age and prior OHE were predictive for both tests but for the Encephalopathy stroop hypertension was found to be independently predictive (Table 1).

CONCLUSION: The diagnosis of CHE can be influenced by other non-cognitive variables and these vary between individual testing strategies probably due to the differential effects that these systemic conditions have on cerebral/subcortical functions. Physicians must take into consideration these covariates while interpreting CHE testing based on these 2 tests.

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Decreased Cognitive Performance Is Associated With Reduced Resting State Connectivity and Gray Matter Atrophy in Patients With Minimal Hepatic Encephalopathy

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[51]
CONCLUSIONS: Decreased cognitive performance is associated with reduced rs-FC and GM atrophy in MHE patients. These changes could have predictive value for detecting MHE. Alterations in the FC of the hippocampal system could contribute to learning and long-term memory impairments in MHE patients. This study shows the association between alterations in learning and long-term memory and structural and FC disturbances in hippocampal structures in cirrhotic patients. Supported by Ministerio Economía, Industria y Competitividad - Instituto Salud Carlos III (FIS PI15/00035; FIS PI18/00150) to CM, Consellería Educación Generalitat Valenciana (PROMETEOII/2014/033, PROMETEOII/2018/051 to VF, CM, ACIF/2018/284 to JG), co-funded with European Regional Development Funds (ERDF).

ABSTRACT: Animal models are essential to investigate the mechanisms responsible for the cognitive and motor alterations in minimal or clinical hepatic encephalopathy (HE). The characterization of these mechanisms allows identifying new therapeutic targets which modulation may improve neurological function in patients. Animal models also allow testing if treatments directed to modulate these targets improve cognitive and motor function. These studies require evaluation of cognitive and motor function in animal models. It is important to understand which tests can be performed in rodents, which cognitive and motor aspects are evaluated by the tests and how they can be related to cognitive and motor dysfunction in the patients. The earliest alterations in patients with minimal HE (MHE) include attention deficits, psychomotor slowing, impairment of visuo-motor and bimanual coordination, of working memory, spatial memory, long-term memory, spatial orientation, verbal learning, concentration, balance and equilibrium, associated with increased falls. To understand the mechanisms involved in each type of cognitive and motor alteration in MHE the behavioral tests in animal models should be designed to evaluate these neurological alterations by procedures that maximize the translatability to the clinic.
human situation and the utility to evaluate treatments to improve cognitive and motor impairment. Many functions are evaluated in humans using pencil or computerized tests such as number connection tests, repetition of series of words or numbers, naming colors, and other actions which can’t be reproduced exactly in animal models. Functions such as verbal learning can’t be evaluated in animal models. However, a good number of cognitive and motor processes impaired in patients with MHE may be evaluated in rodents using appropriate behavioral tests. For example, a combination of properly designed tests in the radial maze, Morris water maze, object recognition and object location allows to be evaluated in animal models. However, a good number of cognitive and motor processes impaired in patients with MHE may be evaluated in rodents using appropriate behavioral tests. For example, a combination of properly designed tests in the radial maze, Morris water maze, object recognition and object location allows evaluating with high sensitivity working memory, reference memory and distinguishing the spatial and non-spatial components of working and reference memory. These components are altered in rats with MHE and different mechanisms are involved in the impairment of different components. Also, there are pharmacological treatments that restore selectively working or reference memory and spatial or non-spatial learning and memory in rats with MHE. There are also appropriate test to assess some motor alterations: hypokinesia, fine motor coordination or balance. Studies based on proper use of animal models will accelerate the advance in understanding the mechanisms involved in MHE and will open new therapeutic approaches to improve quality of life and life span of the patients.

METHODS: Male C57Bl/6 mice were treated with azoxymethane (AOM; 100 mg/kg BW) to induce ALF. Six hours after AOM injection, mice were injected with the TSP-1 antagonist LSKL (30 mg/kg) or SLLK as control. In parallel, male TSP-1 knockout mice and wild-type (WT) controls were injected with AOM. In AOM-treated mice, cognitive impairment was monitored by retention and ataxia measurement. Liver histology was assessed by hematoxylin and eosin staining and serum transaminases were measured. Cleaved caspase 3 immunohistochemistry and TUNEL staining were used to assess apoptosis in liver tissue. Hepatic inflammation was determined by measuring IL-1β, IL-6 and TNFα expression via real-time PCR and ELISA assays. TGFB1 and TSP-1 expression were assessed in liver, serum and cortex by immunohistochemistry, immunohistochemistry and real-time PCR. Cerebral edema and microglia activation were assessed and neuroninflammation was measured by assessing IL-1β, IL-6 and TNFα expression in the cortex. RESULTS: Mice injected with AOM had elevated hepatic, circulating and cortical TGFB1 and TSP-1 levels, with the cortex only having elevated TGFB1. LSKL-treated mice and TSP-1 knockout mice administered AOM had reduced activation of hepatic TGFB1, hepatocyte apoptosis, inflammation, and hepatic injury compared to AOM and SLLK-treated mice or WT AOM-treated mice. LSKL-treated and TSP-1 knockout mice administered AOM had an increased latency to reach coma compared to SLLK-treated or WT mice. LSKL-treated mice and TSP-1 knockout mice had reduced TGFB1 expression, less cerebral edema, attenuated microglia activation, and decreased expression of IL-1β, IL-6 and TNFα in the cortex compared to control mice. CONCLUSIONS: TGFB1 and TSP-1 were elevated in the livers and serum of AOM-treated mice and strategies employed to reduce TGSP-1 signaling reduced liver damage and neuroninflammation in the AOM mouse model of HE. Therefore, targeting TGSP-1 signaling may be a novel therapeutic target for the management of both ALF and HE following acute liver injury.

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**Thrombospondin-1 WorsensAzoxymethane-Induced Hepatic Encephalopathy Through Activation of Transforming Growth Factor Beta 1**

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**BACKGROUND:** Acute liver failure (ALF) is a consequence of severe hepatic injury and is associated with poor clinical outcomes. Patients with ALF often present with neurological complications, called hepatic encephalopathy (HE). Transforming growth factor beta 1 (TGFβ1) is upregulated following liver damage and we have shown that TGFB1 drives HE progression. Thrombospondin-1 (TSP-1) can activate latent TGFB1 and therefore, we hypothesize that hepatic-derived TGFB1 is activated by TSP-1, which exacerbates liver damage and HE associated with azoxymethane-induced ALF.

**METHODS:** Male C57Bl/6 mice were treated with azoxymethane (AOM; 100 mg/kg BW) to induce ALF. Six hours after AOM injection, mice were injected with the TSP-1 antagonist LSKL (30 mg/kg) or SLLK as control. In parallel, male TSP-1 knockout mice and wild-type (WT) controls were injected with AOM. In AOM-treated mice, cognitive impairment was monitored by retention and ataxia measurement. Liver histology was assessed by hematoxylin and eosin staining and serum transaminases were measured. Cleaved caspase 3 immunohistochemistry and TUNEL staining were used to assess apoptosis in liver tissue. Hepatic inflammation was determined by measuring IL-1β, IL-6 and TNFα expression via real-time PCR and ELISA assays. TGFB1 and TSP-1 expression were assessed in liver, serum and cortex by immunohistochemistry, immunohistochemistry and real-time PCR. Cerebral edema and microglia activation were assessed and neuroninflammation was measured by assessing IL-1β, IL-6 and TNFα expression in the cortex. RESULTS: Mice injected with AOM had elevated hepatic, circulating and cortical TGFB1 and TSP-1 levels, with the cortex only having elevated TGFB1. LSKL-treated mice and TSP-1 knockout mice administered AOM had reduced activation of hepatic TGFB1, hepatocyte apoptosis, inflammation, and hepatic injury compared to AOM and SLLK-treated mice or WT AOM-treated mice. LSKL-treated and TSP-1 knockout mice administered AOM had an increased latency to reach coma compared to SLLK-treated or WT mice. LSKL-treated mice and TSP-1 knockout mice had reduced TGFB1 expression, less cerebral edema, attenuated microglia activation, and decreased expression of IL-1β, IL-6 and TNFα in the cortex compared to control mice. CONCLUSIONS: TGFB1 and TSP-1 were elevated in the livers and serum of AOM-treated mice and strategies employed to reduce TGSP-1 signaling reduced liver damage and neuroninflammation in the AOM mouse model of HE. Therefore, targeting TGSP-1 signaling may be a novel therapeutic target for the management of both ALF and HE following acute liver injury.

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BACKGROUND: Predicting overt hepatic encephalopathy (OHE) is of major importance because the condition is unpleasant, requires hospitalization, and partly preventable. The risk is related to prevalent existing discrete cognitive defects, and a number of psychometric tests are validated for detection of such defects. For clinical practice it is recommended to apply two different tests. We used the Continuous Reaction Time test (CRT) and the Porto Systemic Encephalopathy Test (PSE), and examined their single and combined value for prediction of OHE in cirrhosis patients.

METHODS: We studied 130 mentally unimpaired cirrhosis patients by the two tests and followed them up for an average 38.5 months. The CRT measures velocity and stability in motor reaction times to 150 repeated auditory. The PSE is a paper-and-pencil test measuring the duration of completing 5 tasks. We collected data on episodes of OHE during follow-up. The clinical course was analysed in patient groups according to the outcome of each test and of both tests together. No anti-HE treatment was initiated except for OHE.

RESULTS: We observed 74 OHE events. The PHE was abnormal in 47 and predicted 31 OHE episodes among 14 patients (PPV = 29%, NPV of 75%, sens. 48%, spec. 65%). The CRT test was abnormal in 74/130 and predicted 54 OHE episodes among 23 patients (PPV = 31%, NPV = 78%, sens. 65%, spec. 46%). One or both tests were abnormal in 87/130 and predicted 60 OHE episodes among 27 patients (PPV = 31%, NPV = 81%, sens. 77%, spec. 48%). 43/130 had two normal tests but 8 experienced OHE and had 14 OHE-admissions.

CONCLUSIONS: The combined use of PSE and CRT test identified 77% of patients who later experienced OHE while ruling out future OHE with an NPV of 81%.

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Supplementation With Synbiotics and/or Branched Chain Amino Acids in Hepatic Encephalopathy: A Pilot Randomized Placebo-Controlled Clinical Study
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BACKGROUND: Hepatic encephalopathy (HE) is common in patients with cirrhosis and characterised by reduced hepatic ammonia clearance. This is accompanied by alterations in gut bacteria and increased intestinal epithelial permeability that may be ameliorated with synbiotics (pro- and pre-biotics). Branched chain amino acids (BCAAs) are thought to have a role in the detoxification of ammonia. We investigated the effects of the administration of Synbiotics and/or BCAAs in treating HE.

METHODS: Methods Participants with minimal HE (MHE) were randomised in an placebo-controlled study to receive synbiotics, BCAAs, or a combination of BCAAs and Synbiotics. The investigators were blinded to the supplements at all times. Relevant biochemical and nutritional data and depression and anxiety scores (DASS-21) were collected at entry, 4 weeks, and on completion, at 8 weeks. The Trail Making Test (TMT) and Inhibitory Control Test (ICT) were used to assess cognitive function in HE. Results were analysed using linear mixed effects regression analyses.

RESULTS: Sixty-one participants with MHE determined by the treating physician, confirmed on psychometric testing (TMT and ICT) and who were taking 63 ± 6 mls lactulose/day were enrolled. Recruitment was limited by the widespread introduction of rifaximin in Australia during the recruitment period. The final intention to treat analysis included 49 participants who returned for at least 1 follow-up review. The mean age was 55.1 ± 6.1 years and 86% were males. Despite evidence of a placebo effect, there was significant improvement in TMT B (P ≤ 0.05) (Figure 1a) and ICT weighted lures (P = 0.007) (Figure 1b) in participants who received combined synbiotics/BCAAs treatment compared to placebo at study completion. Cognitive improvement occurred without a significant change in ammonia levels.

CONCLUSIONS: To the best of our knowledge, this study is the first to report an improvement in cognitive function and, therefore, executive function in individuals with uncomplicated cirrhosis and MHE in response to oral supplementation with combined synbiotics and BCAAs. A larger study which includes measures of dysbiosis and intestinal epithelial permeability is needed to confirm these results.

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Characterization of a Novel Mouse Model of Type A Hepatic Encephalopathy
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BACKGROUND: Type A hepatic encephalopathy (HE) describes the neurological complications caused by acute liver failure. Research into Type A HE has been hampered as existing models cause severe and rapid HE, with a limited therapeutic window and high mortality, that do not reflect all features observed in patients. The aim of this study was to establish and characterize an alternative mouse model of Type A HE that has a more protracted timeline of pathology.

METHODS: Male C57Bl/6 mice were fed standard rodent chow enriched with 0.1% 3,5-diethoxycarbonyl-1,4- dihydronicotinamide (DDC) and 10% ammonium acetate (DNC + NH4). Neurobehavioral indices and neuromuscular deficits observed in patients. The clinical course was analysed in patient groups according to the outcome of each test and of both tests together. No anti-HE treatment was initiated except for OHE.

RESULTS: DDC + NH4 feeding caused significant neurological and neuromuscular deficits in every test performed commencing after 3–7 days of feeding. The liver damage observed was like a cholestatic....
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Attenuation of Neurological Symptoms of Type C Hepatic Encephalopathy by Selective Ablation of Neuronal FXR Expression

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BACKGROUND: Hepatic encephalopathy (HE) describes the neurological deficits that result from liver impairment. Liver disease is associated with an increase of circulating bile acids that can cross the blood brain barrier and activate FXR receptors in neurons. We have previously demonstrated that aberrant bile acid signaling via activation of neuronal FXR contributes to HE pathogenesis in rodent models of acute liver failure. However, a role for FXR-mediated bile acid signaling in HE due to chronic liver cirrhosis is undefined.

METHODS: Neuron-specific FXR knock out mice were generated by crossing Floxed FXR mice (FXRflcKO) with SNAP-25 cre recombinase mice. The resulting mice were designated FXRneu. WT and FXRneu were treated with carbon tetrachloride (CCl4; 1 ml/kg) by oral gavage twice per week for 12 weeks. Neurobehavioral indices and neuromuscular disorders were assessed by open field test, rotarod, grip strength test and gait analysis. After 12 weeks, tissue was collected and liver damage was assessed by serum chemistry and H&E staining. Total bile acid content was assessed in the cortex and cerebellum using chromatographic assays. The expression of ASBT, FXR, and its downstream effector SHP was assessed by qPCR and immunofluorescence. Microglia activation was assessed by Iba1 immunofluorescence. The expression of proinflammatory cytokines was assessed by qPCR and ELISA. In parallel, total bile acids, ASBT and FXR expression were assessed in brain tissue from cirrhotic patients with HE, compared to cirrhotics without HE and age- and gender-matched controls that had been collected and banked by the Australian Brain Bank Network.

RESULTS: Total bile acid content was elevated in the cortex and cerebellum in CCl4-treated WT mice and in cirrhotic patients with HE, compared to cirrhotics without HE and non-liver impaired controls. Furthermore, ASBT, FXR and SHP expression were increased in the frontal cortex of mice and humans with HE, but not in non-HE control samples. WT and FXR mice treated with CCl4 had significant deficits observed in every neurobehavioral and neuromuscular test performed, as well as masked microglia activation and increased proinflammatory cytokine expression compared to vehicle-treated mice. These neurological deficits and neuroinflammation were attenuated in FXRneu mice after CCl4 treatment, even though liver damage was comparable in all genotypes of mice used.

CONCLUSIONS: These data indicate that neuronal expression of FXR plays an important role in the development of HE. Specific targeting of FXR activation in the brain may be a potential therapeutic target for the management of HE.

Neurometabolism in Grey Matter of Children With Chronic Liver Disease or Portosystemic Shunting: A 1H-MRS Study at 7T

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BACKGROUND: Neurocognitive deficits in children with chronic liver disease (CLD) or congenital porto-systemic shunts (CPSS) are incompletely understood. Understanding the molecular underpinnings by non-invasive means could inform management. Aims To characterize the neuro-metabolic profile in the grey matter (GM) of children with CLD or CPSS and analyze correlations with neurocognitive and biological results.

METHODS: Children aged 8–14 y were enrolled if they presented with CLD or CPSS. Short-echo time (16 ms) using 1H-MRS at 7T in GM dominated medial prefrontal cortex was performed, and neurocognitive testing and routine labs were obtained within 3 months of each other following informed consent.

RESULTS: 5 patients (8–14 y) including 4 with CLD (2 girls), 1 with CPSS (1 girl), and 4 controls (10–14 y, 2 girls) underwent 1H-MRS. Causes of CLD: congenital disorder of glycosylation (1), progressive familial intrahepatic cholestasis type-2 (1), portal obliterative venopathy (1), autoimmune hepatitis (1). Mean plasma ammonium in patients was 26 µmol/L, mean serum bilirubin was in normal range and mean platelet count was 201 G/L (59–346). The 3 patients with CLD showed scores in average or above average on Total Intellectual Quotient measures (WISC-IV). One of the 3 scored below average on the working memory sub-scale of the WISC-IV. One of the 3 scored below average in the working memory sub-scale of the WISC-IV (<1, 65 SD), while the intellectual profiles were homogenous and above average for the 2 other patients. One of these 2 scored below average on 6/10 parameters on the Conners Continuous Performance Test, suggesting attention deficit. The other two were in range. The patient with CPSS displayed Total Intellectual Quotient below average (<1, 65 SD on the WISC-IV), with additional deficits (<1, 65 SD) in executive and attentional functioning as well as expressive and receptive language. 1H-MRS results: 13 metabolites were reliably quantified. Figure 1 illustrates the differences between CLD and CPSS: the expected increase of brain glutamine and decrease of brain osmoles (insol, taurine, total choline) together with
ammonia >50 μmol/L, MRI T1 hyperintensity of the basal ganglia and an MRS HE profile sug- gestive of HE were all statistically associated with the diagnosis of MHE (P < 0.0001). The best diagnostic performance was achieved by combining MRS with either MRI T1 hyperintensity (AUC = 0.93) or ammonia (AUC = 0.91).

CONCLUSION: A multimodal approach combining clinical data, ammonia and cerebral MRI with MRS seems to have good accuracy for the diagnosis of MHE. Further prospective studies are mandatory.

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Drug-induced Hyperammonaemia: Data From Vigibase, the WHO Database

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BACKGROUND: Altered consciousness secondary to metabolic encephalopathies represents a major cause of ICU admission with favorable outcome when diagnosed and treated rapidly. Ammonia dosage is thus recommended in most textbooks in the absence of any diagnosis after etiological work-up encompassing biological sampling, cerebral imaging and EEG. Despite hyperammonaemia is most commonly secondary to liver diseases, portosystemic shunts, inborn errors of metabolism, mostly by urea cycle defects, microbial pulsation or drug-induced hyperammonaemia (DH) are other possible causes. DH is poorly described but it is mainly recognized as the consequence of valproic acid. Some antineoplastic agents, fluorouracil or asparaginase, have been implicated but this class is evolving rapidly. To describe the drugs associated with DH.

METHODS: We used Vigibase, the WHO global Individual Case Safety Report (ICSR) database, which contains reports of suspected adverse drug reactions (ADRs) collected by national drug authorities in over 130 countries between 1967 and 8 May 2019. This observational retrospective study included all ADRs reported as ‘hyperammonaemia’ according to the Medical Dictionary for Drug Regulatory Activities (MedDRAv21.1) term (Preferred term [PT] level). The drugs consid- ered in the analysis were those notified as suspected treatments. Drugs used to treat hyperammonaemia or hepatic encephalopathies were excluded as were drugs reported less than 3 times. Drugs with a positive lower end of the 95% credibility interval for the information component (ICO25) > 0, an indicator value for disproportionate Bayesian reporting, was considered as causative of hyperammonaemia.

RESULTS: Among 19 438 165 ICSRs, 576 drugs were identified for the term ‘hyperammonaemia’ [PT]. Six were excluded because they were used to treat hyperammonaemia or hepatic encephalo- pathy. Thus, 73 drugs had an ICO25 > 0 and represented 2759 cases (0.014%). Twelve drugs were reported more than thirty times (Table 1).

CONCLUSION: Besides commonly involved drugs, some other commonly used drugs seem asso- ciated in DH. These data could help in the etiological work-up of hyperammonaemia.

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Increased Levels of Xenobiotics in Plasma of Cirrhotic Patients With Neurological Symptoms, A Metabolomic Study

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BACKGROUND: Encephalopathy is a classical complication of liver disease and/or portosystemic shunts. Its pathophysiology is not completely elucidated; mechanisms include the role of elevated ammonia levels in association with systemic inflammation. An impairment of blood-brain barrier (BBB) permeability is also hypothesized. Metabolomics enables to detect a wide range of metabolites without any a priori. In a recent metabolomic study including patients who underwent cerebrospinal fluid (CSF) collection, our group outlined that xenobiotics/drugs that usually are not able to cross BBB were retrieved in the CSF, suggesting a potential neurological toxicity of drugs. CSF collection is invasive. To describe the xenobiotics present in the plasma of cirrhotic patients, using the same metabolomic approach.

METHOD: We conducted a retrospective study of plasma samples in the Hepatological IC3. Plasma samples from cirrhotic patients displaying encephalopathy were compared to plasma from cirrhotic patients without neurological symptoms, and to plasma from healthy controls. Liquid chromatog- raphy coupled to high-resolution mass spectrometry was performed and thereafter the metabolite fingerprints were compared to database and between the different groups.

RESULTS: Plasma samples were obtained from 12 cirrhotic patients with encephalopathy (age 59 [40–68], MELD 20 [16–31], alcohol 58%), 13 cirrhotic patients without encephalopathy (age 56 [55–64], MILD 17 [14–29], alcohol 38%) and 9 healthy controls. Among 495 identified metabolites, the previously unreported decrease in the neurotransmitters glutamate, GABA and N- acetylaspartate. No statistically significant differences were observed between the CLD patients and controls.

CONCLUSIONS: In patients with compensated CLD, there were no significant neuro- metabolic alterations as assessed by high resolution 1H-MRS. In CPSS, however, neuro- metabolic changes were clear, and likely related to measurably impaired neurocognitive functioning. Together, these results suggest that in CPSS (type B encephalopathy) the brain is likely exposed to a higher load of neurotoxic substances than in patients who have some degree of portal flow (type C).
Hippocampal and Cerebellar Astrocytes Morphological Alterations in a Rat Model of Chronic Hepatic Encephalopathy

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BACKGROUND: Chronic hepatic encephalopathy (CHE) is a spectrum of neuropsychiatric abnormalities in patients with chronic liver disease. The hippocampus and cerebellum are key regions implicated in the cognitive and fine motor deficits of CHE. Astrocytes can sense neuronal activity through neurotransmitter-receptors and ion-channels, modulate the neural circuits, and control energy homoeostasis through morphological plasticity. They adjust their volume by releasing osmotyes (inositol, taurine, creatine) and can remodel their processes.1-4 They initiate synaptic development and regulate synaptic plasticity in both the healthy and injured brain.5 Astrocytes convert the neurotoxin ammonia into glutamine, regulate cerebral hemodynamics and cytokine responses to inflammatory reactions and creation of glial-scar, something to be investigated in future studies. Finally, the astrocytosis and astrocyte morphology changes may alter the CNS microenvironment that usually ensures neuronal health and may contribute to the cognitive impairment of BDL rats.

METHODS: BDL-rats and sham-rats at 4 and 8-weeks post-BDL (n = 3/group/2-time-points) were anesthetized with 4% isoflurane and Temgesic (ESSEX) 0.1mg/kg before transcardial PBS perfusion. Brains were fixed in 4%-formaldehyde and cryopreserved in 30%-sucrose, embedded in a Tissue-Tek®OCT. Immunohistochemistry: On 16 micron sagittal-sections, GFAP7 and DAPI (nucleus) were used. For each rat (n = 16/group) 20 sections were analyzed (distance between sections 200 microns). Morphometric measurements were performed using Sholl-analysis.8

RESULTS: Astrocytes activation is represented by the significant increase in GFAP+ cells at week4 post-BDL in the hippocampus (+47.5%) and cerebellum (+48.7%) vs SHAM (Figure 1a,b). Decrease in the processes intersection was observed already at week4 post-BDL (Figure 1e). Although at week8 post-BDL a significant reduction of astrocytes number was observed (~20%) (Figure 1b) the astrocytes were altered morphologically, showing shortening (hippocampus: week 4 – 13.3%, week 8 – 32.4%; cerebellum: week 4: ~17.3%, week 8: ~35.5%) and decreased number of processes (hippocampus: week 4: ~5.8%, week 8: ~18.77%; cerebellum: week 4: ~32.2%, week 8: ~41.5%) and processes intersections at week 8 post-BDL (hippocampus: ring1: ~14.5%, ring 2: ~39%, ring 3: ~72.5%; cerebellum: ring1: ~17.6%, ring 2: ~27.4%, ring 3: ~58.7%) as well as minor processes thickening (Figure 1d). The reported % changes are relative to SHAM.

CONCLUSIONS: To our knowledge, this is the first report showing significant alterations in astrocytes count and important morphological changes already 4-weeks post-BDL in the hippocampus and cerebellum. Increase in GFAP+ cells may be related to the stimulation of mature astrocytes and reentering into proliferation cycle which is similar to proliferating neonatal astrocytes and is a common situation in various neuropathological disorders.5-7 The proliferation of activated glial-cells can induce additional inflammatory reactions and creation of glial-scar, something to be investigated in future studies. Finally, the astrocytosis and astrocyte morphology changes may alter the CNS microenvironment that usually ensures neuronal health and may contribute to the cognitive impairment of BDL rats.

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Brain Regional Susceptibility to Oxidative Stress in a Rat Model of Chronic Hepatic Encephalopathy: In-Vivo 1H MRS, Ex-Vivo ESR Spectroscopy and Histology Findings

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BACKGROUND: Oxidative stress (OS) is believed to be an important feature in the pathogenesis of chronic hepatic encephalopathy (CHE).1 In CHE impaired ammonium clearance by the diseased liver leads to brain glutamine accumulation. In-vitro, affected ammonium detoxification together

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**Fig. 1**  
A) Representative micrographs of double staining for anti-GFAP (red) and DAPI (blue) of the hippocampus of sham, BDL w4 and BDL w8 post-op rats, scale bar: 500μm.  
B) Astrocytes density quantification at the hippocampus hilus and cerebellum granular layer. Note the increase in astrocytes number at week 4 post BDL, two way-Anova: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, mean±SD.  
C) Astrocytes Sholl analysis – morphological characterization of the number of intersections of processes branches with radii at various distances from the cell body.  
D) Representative micrographs of brain sections from sham and BDLs rats at 4 and 8 weeks post-op stained with anti-GFAP (red) and DAPI (blue), scale bar: 25μm.  
E) Sholl analysis of GFAP-labelled astrocytic intermediate filaments (IMF) showed a significant time dependent decrease of the number of processes, intersections (decrease of intersections in each of the three concentric rings) and the mean length of the IMF observable within the section, two way-Anova:*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, mean±SD.
**A) In-vivo ¹H-MRS – antioxidants detection as indirect OS sign**

- **Hippocampus**
  - Gln (green) and Asc (blue) levels over time.
  - GSH (pink) levels over time.
- **Cerebellum**
  - Gln (green) and Asc (blue) levels over time.
  - GSH (pink) levels over time.

**B) EX-vivo ESR – direct OS detection**

- **ESR Silent CM-H**
  - CO₂⁻ + OH⁻ → 1.2x10⁶ M⁻¹ s⁻¹
- **ESR Active CM**
  - 3H₂O₂ + H⁺ → H₂O + 2H⁺

**C) IHC staining with GPX1 - anti-oxidative enzyme**

**Fig. 1 A)** Evolution of Gln, Asc and GSH, from week 0 (before BDL) to week 8 post-BDL. **B)** Cell permeable-non-toxic spin probe for the quantification of extra and intracellular O₂⁻ production and detection of ROS. The spin adduct is resistant to reduction by vitamin C (Asc) and thiols (GSH), therefore allows to quantitative detection of O₂⁻. ROS generation rate is calculated from ESR kinetics plots. **C)** Photomicrographs of histological sections of cerebellum – immunohistochemical staining of GPX1 on 10μm sections showed increased immunoreactivities in Purkinje and granular cells layer of BDL rat (arrowhead – Purkinje cells layer, arrow – granular cells layer, * – molecular layer and WM – white matter). Purkinje cells of BDL rat revealed shrinking soma having the mean size of 8.04±1.8μm² while the size of Sham is 12.5±1.2μm² (p<0.00001). Two way-Anova: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, mean±SD.
with glutamine induces reactive-oxygen-species (ROS) generation associated with astrocyte impairment. 2-3 ROS play an important role in cellular signaling, synaptic plasticity, learning and memory. When in excess, they cause cellular damage. 4-5 Systemic oxidative stress was previously shown in bileduct-ligated rats (BDL). Using in-vivo-longitudinal 1H-MRS we previously observed the indirect presence of OS as a decrease of brainAsc in the hippocampus and cerebellum of BDL rats (model of CHE). 6 We aimed to validate these findings using for the first time ex-vivo electron spin (ESR) spectroscopy and histological measures to assess OS levels.

METHODS: In-vivo-1H-MRS: Cerebellum/hippocampus of adult rats were scanned before BDL and after every 2-weeks up to week 6 (n = 18) at 9.4T-MRI (Varian/Magnet Sci.). Using SPECIAL-sequence 7 (TE = 2.8 ms). Ex-vivo-ESR: ESR300e Bruker Biospin was used for in-travascular superoxide anion detection. Hippocampus/cerebellum were extracted at 6weeks post-BDL/sham-surgery (n = 9), incubated in medium with 10 mM-CMH-cell-permeable spin-trap (Nonyum GmbH). Immunohistochemistry (IHC) GPX1 (anti-oxidative-enzyme) staining was performed (n = 6).

RESULTS: The increase in plasma NH4+ and bilirubin confirmed the presence of chronic liver disease. A ~80% increase in brain glutamine was measured at week 4, while Asc showed a stronger decrease in cerebellum (~32% at week 5, P < 0.001) (Figure 1a). ESR revealed differences in redox state between the two brain regions (~31% higher in cerebellum, P < 0.004) (Figure 1b). However, the relative change in both brain regions and sham was similar ~42%. The significant increase of hippocampal/cerebellar OS in BDL (P < 0.01, P < 0.001) corroborate the 1H-MRS findings of decreased Asc concentrations (Figure 1a). IHC with GPX1-enzyme~4,5 revealed an increase activity in Purkinje and granular cell-layer of BDL cerebellum (Figure 1c). Purkinje-cells also showed shrinking soma (BDL: 8.04 ± 1.8 μm², sham: 12.5 ± 1.2 μm², P < 0.0001). Elevated GPX1 in cerebellum suggests that GSH-synthesis may increase (confirmed by increased GSH in 1H MRS, Figure 1a) in response to OS-related injury. Elevated OS might suggest that ROS could lead to brain functions disruption. 10-12

CONCLUSIONS: Our results showed for the first time the presence of central OS in BDL rats at 6-weeks post-surgery. Changes varied according to brain region and proved a different susceptibility of cerebellum and hippocampus to CHE, reflected by a relationship between increased OS and intact antioxidant-defence-system. OS is involved in the propagation of cellular injury and may be an important factor in the aetiology of the CHE.

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Sarcopenia Pre- and Post-liver Transplantation: Implication for Hepatic Encephalopathy

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BACKGROUND: Muscle wasting (sarcopenia) and hepatic encephalopathy affect 30 to 70% of cirrhotic patients. The presence of sarcopenia may be associated with a worse prognosis and complications, including hepatic encephalopathy, in cirrhotic patients awaiting and after liver transplantation. To this day, few studies have evaluated and followed muscle mass (in terms of quantity and quality) after LT. The goal of this study was to assess the association between the evolution of sarcopenia and the prognosis of cirrhotic patients, including hepatic encephalopathy and neurological complications, before and after LT.

METHODS: In total, 94 cirrhotic patients who underwent LT at the Montreal University Hospital Center - Liver Unit were included. Sarcopenia was assessed at the third lumbar lever vertebrae using a computed tomography scan (CT-scant). The diagnostic of sarcopenia was based on previously established sex-specific cut-off values of skeletal muscle index. Patients were classified into two groups (1) persistent or newly developed sarcopenia after LT (Sarc+); (2) resolved sarcopenia or absence of sarcopenia before and after LT (Sarc−). Muscle quality (myosteatosis) was assessed by calculating intramuscular adipose tissue content. The prognostic factors were collected 6 months before and during 1 year after LT through medical records and included the number of complications, the presence of hepatic encephalopathy and the episodes of infections, the length of stay, and the frequency of readmissions.

RESULTS: Sarcopenia persisted or was newly developed (Sarc+) in 62% of the patients (n = 58). It remained absent or was resolved after LT in 38% of the patients (n = 35). Muscle quality was significantly decreased post-LT (P = 0.034). The group Sarc− experienced more complications pre-LT (P = 0.001). The group Sarc+ had infections post-LT (P = 0.001) and readmissions (P = 0.048) compared to the group Sarc−. The length of stay was longer for the group Sarc+ as opposed to the group Sarc− (P < 0.001). Hepatic encephalopathy was present in 83% of patients pre-LT whereas 17% experienced persistent neurological complications post-LT.

CONCLUSIONS: Persistent and newly developed sarcopenia after LT appear to have negative outcomes on the prognosis of patients. Interventional strategies to optimize, increase or preserve muscle mass could help to improve post-operative recovery as well as the quality of life in patients who have undergone LT.

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Quality of Life Assessment May Aid in the Diagnosis of Minimal Hepatic Encephalopathy and Prediction of Overt Hepatic Encephalopathy

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BACKGROUND: Minimal hepatic encephalopathy (MHE) impinges on quality of life (QoL), is associated with a high risk of overt hepatic encephalopathy (OHE) and is often treatable by simple means. Still, MHE is rarely systematically diagnosed and treated likely because dedicated psychometric tests give the impression of being resource heavy and thus scare off many clinicians. Simple, patient-administered QoL questionnaires e.g. sickness impact profile (SIP), could improve diagnostic rates. This approach was tested in a US-based study introducing SIP/CHC score (formula of 4 SIP statements, gender and age). We here aim at externally validate SIP/CHC score in a cirrhotic cohort using continuous reaction time (CRT) test and postpsychometric hepatic encephalopathy score (PHES) for MHE diagnosis.

METHODS: 110 cirrhotic patients without OHE (age 60 years, MELD 11.4, 80% blue-collar) completed cognitive testing and SIP. Abnormal CRT and/or PHES diagnosed MHE. SIP consists of 136 questions inquiring about QoL and standardized QoL scores were compared in MHE and non-MHE patients. The SIPCHE (US derived) was applied as a predictive values were calculated. We followed the patients for 2.7 years on average and registered OHE episodes.

RESULTS: The SIP/CHC was abnormal in 82/110 patients and was in agreement with the psychometric tests in 7/91/10 cases (66%). The SIP/CHC indicated MHE in 58/71 of the patients with MHE according to 2-3 CRT psychometry (positive predictive value = 71%, specificity = 82%, AUCROC 0.68). The SIP/CHC was false positive in 24/39 non-MHE patients (positive predictive value 38%, NVP 53%). A normal SIP/CHC did not exclude MHE in our population as 13/28 (46%) with a normal SIP/CHC score had MHE according to the CRT and PSE tests. In our cohort using a cut-point of ~0.40, in stead of >0.60, slightly improved correct classification to 72% of patients. Only 42/14% (8) with a normal basalline SIP/CHC experienced OHE, while 29/82 (30%) with abnormal SIP/CHC experienced OHE (P = 0.05). Accordingly, the SIP/CHC positive predictive value for a future HE episode is this 87% (likelihood ratio 2.4).

CONCLUSIONS: In conclusion, the idea of a patient-reported outcome score as an addition to standard psychometry is appealing. The US derived SIP/CHC score is able to identify the majority of patients with MHE and future OHE episodes, but lacks diagnostic specificity. We predict that development of regional SIPCHE scores could be useful. In future studies using the SIPCHE as a measure of patients-experienced effect of MHE treatment would be of interest.
Figure 1: Principal Component Analysis showing faecal cytokines vs patients grouped by stable cirrhosis or acute decompensation – scores and loading plots

![Figure 1](image-url)

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Acetate Attenuates the Astrocyte Swelling and Brain Edema in Severe Liver Failure
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**BACKGROUND:** Astrocyte swelling and brain edema are major complications of severe liver failure. Ammonia plays a major role in the development of astrocyte swelling/brain edema in this condition. However, current therapies have not thus far improved the outcome of liver failure induced astrocyte swelling/brain edema. Since acetate has been shown to have neuroprotective effect in other neurological conditions, likely through increased energy production, we examined whether acetate similarly protects cell swelling in cultured astrocytes post-ammonia exposure. We also examined whether treatment of rats with gyceryl triacetate (GTA), an acetate precursor, which is known to increase circulating, as well as tissue levels of acetate, alleviates the brain edema induced by the liver toxin thioacetamide (TAA).

**METHODS:** Astrocyte cell volume was estimated by measuring the intracellular water space using 3-O-methylglucose. Brain water content was measured by using the gravimetric method.

**RESULTS:** Exposure of astrocyte cultures to pathological concentrations of ammonia (NH4Cl, 5 mM) for 24 h significantly increased cell swelling. Co-treatment of ammonia with acetate reduced such swelling in a dose-dependent manner. Further, treatment of rats with TAA (250 mg/kg bw) for 3 days increased the brain water content, and that pretreatment of (intragastrically) TAA-treated rats with GTA (7.5 g/kg bw) attenuated brain edema.

**CONCLUSIONS:** These findings strongly suggest that acetate supplementation will exert salutary effects in reducing brain edema in patients with severe liver failure.

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Cholestasis Decreases Dendritic Spine Density in a Rat Hippocampal Organotypic Culture
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**BACKGROUND:** Executive functioning impairment in children with cholestasis liver disease is increasingly recognized. Injury to developing neuronal networks could be an underlying mechanism. Given that the CSF of rat pups following biliary duct ligation is highly concentrated in ammonia, muricholic and taurocholic acids, we hypothesized that cholestasis may significantly alter density of synaptic contacts onto pyramidal neurons, known to be essential in the development of executive functioning.

**METHODS:** Hippocampal organotypic slice (400 μm thick) was isolated from 4–5-day-old Wistar rats. They were maintained for 15 days in a CO2-incubator (33°C). pc-DNAs1-EF1GF plasmid biolistic transfection was performed 7 days after harvesting. 3 days following transfection, control medium or experimental medium containing 100 μM o-methylglucose. Brain water content was measured by using the gravimetric method.

**RESULTS:** Static analysis quantified dendritic spines turnover (loss and neo-formation) for each 24 h time-window. Statistical analysis was conducted using PRISM software for multiple t-test or mixed-effect ANOVA.

**RESULTS:** Static analysis showed a biphasic profile in MIX condition. During early phase (first 3 days of exposure), we observed >50% decrease in dendritic spine density compared to control (cf Figure 1, P < 0.001). On days 3 to 4, spine density recovered to reach control value. Dynamic analysis showed 15% loss in dendritic spines stability during the early phase of exposure to MIX condition, compared to controls, with comparable low rates of spine turnover. During the late phase of MIX exposure, spine turnover increased significantly in favor of spine neo-formation: spine neo-formation was 10 times higher (0.280 vs 0.033 spines/μm2, P = 0.0033) than controls, while spine loss was 6 times higher in neurons exposed to MIX (0.154 vs 0.026 spines/μm2, P = 0.00026) than controls.

**CONCLUSIONS:** We demonstrate here that mimicking cholestasis ex vivo leads to a biphasic response in spine density of rat hippocampal CA1 pyramidal neurons. Spine density decreases during...
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Reversible and Irreversible Neurological Complications in Hepatic Encephalopathy
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BACKGROUND: Hepatic encephalopathy (HE) is a major neurological condition that occurs due to acute and chronic liver failure following drug toxicity, viral hepatitis, or exposure to various hepatotoxins. Acute HE (Type A HE) is associated with cerebral edema, increased intracranial pressure, coma and death. Chronic HE (Type C HE) is characterized by mental confusion, behavioral changes, and motor disturbances. It is currently unclear whether HE is reversible or irreversible. We therefore examined whether acute or chronic liver failure is reversible or irreversible in the thioacetamide (TAA) rat model of acute and chronic HE. Accordingly, rats were treated with the liver toxin TAA and brain edema, neurobehavioral, cognitive and motor deficits were measured.

METHODS: Rats were treated with the liver toxin TAA and brain edema, neurobehavioral, cognitive and motor deficits were measured.

RESULTS: Treatment of rats with high doses of TAA (to induce acute HE) led to brain edema within 2-3 days. Rats following TAA treatment were examined for longer time periods. Rats did not exhibit any brain edema, although they expressed neurobehavioral, cognitive and motor deficits without any changes documented in blood and brain ammonia levels, as well as liver failure markers, as compared to normal rats. However, rats that underwent chronic liver failure for 10 days displayed neurobehavioral, cognitive and motor deficits, along with brain structural and molecular events, including reduced levels of astrocytic matrix proteins, as well as reduced levels of neuronal proteins. We also found a reduction in synaptic density and in dendritic complexity. These changes correlated well with increased blood/brain ammonia levels and with liver failure markers. However, when TAA treatment was withdrawn (after 10 days), and the rats monitored for longer time periods still showed neurobehavioral, cognitive and motor deficits, as well as deficient neurological integrity, even though blood and brain ammonia levels, as well as liver biochemical and molecular parameters were reversed.

CONCLUSIONS: These findings strongly suggest that neurobehavioral, cognitive and motor deficits in HE cannot be reversed even when acute or chronic liver failure had been corrected.

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The Contribution of the Blood-Brain Barrier and Choroid Plexus to the Pathology of Hepatic Encephalopathy
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ABSTRACT: Cerebral edema and associated increase in intracranial pressure, along with brain herniation are the major complications found in patients with acute liver failure (Type A HE or acute hepatic encephalopathy, AHE) which represents the most frequent cause of death in these patients. The preponderance of experimental evidence favors a cytotoxic mechanism, and the only cell in brain that undergoes such swelling are astrocytes. While there is no evidence of blood-brain barrier break-down as in patients or in experimental animals with AHE, it is unclear how a sustained astrocyte swelling (cytotoxic brain edema) occurring in AHE, ultimately results in increased intracranial pressure, brain herniation and subsequent coma and death in these patients. A major brain component that may be involved in the edema development is the choroid plexus, since epithelial cells of the choroid plexus produce cerebrospinal fluid. Under CNS pathological conditions, the barrier function of blood-CSF barrier is altered, along with changes in the ependyma, leading to a seepage of fluid out of the ventricular system, ultimately resulting in brain edema, along with the entry of inflammatory cells into the brain parenchyma. In preliminary studies, we found activated mast cells in the choroid plexus of the liver toxin thioacetamide (TAA)-treated rats, and such activation significantly increased cytokine production, histamine release and decreased levels of growth factors including platelet derived growth factor, insulin-like growth factor, fibroblast growth factor. We also found increased levels of the water channel proteins aquaporin 1 and 4 (AQP-1/AQP-4) in TAA-treated rat brain choroid plexus, and increased brain edema, while inhibition of inflammation and AQP1/4 expression, which ultimately contributes to the sustained cytotoxic brain edema found in AHE. We anticipate that studies aimed at a better understanding of the role of choroidal plexus inflammatory events in the development of brain edema associated with AHE will greatly facilitate the identification of agents capable of ameliorating this debilitating condition.

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Mechanism of Alzheimer Type II Astrocyte Development: Implication for the Defective Neurological Integrity and Neurobehavioral Deficits Associated With Chronic Hepatic Encephalopathy
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BACKGROUND: Chronic hepatic encephalopathy (CHE) is a major neurological condition that occurs following chronic liver failure (CLF) following drug-induced hepatotoxicity, viral hepatitis, or exposure to various hepatotoxins. CHE is characterized by mental confusion, behavioral changes, and motor disturbances. The molecular basis for CHE remains elusive. The presence of Alzheimer type II
the development of adjunct therapies to manage the neurological complications of acute liver failure.

RESULTS: We identified increased levels of astrocyte gliu maturation factor (GMF), a factor strongly implicated in neuroinflammation and in the overexpression of various inflammatory factors (IL-1β, TNF-α, IL-6, chemokine (C-X-C motif) ligand 1 (CXCL1), matrix metalloproteinase-3 (MMP-3), prostaglandin E2 (PG2) and cyclooxygenase 2 (COX2), as well as reduced levels of α-tubulin and glial fibrillary acidic protein, along with increased levels of aggregated protein lattice α/α in the thioacetamide-induced rat model of CHE. Further, we identified reduced levels of neuronal proteins, PSD95, synaptophysin, and NMDA-m. Moreover, synaptic density and dendritic complexity were reduced post-CLF. Since elevated blood-brain ammonia levels have been strongly implicated in the pathogenesis of CHE, while exposure of cultured astrocytes to ammonia was shown to develop AT2A, we utilized this in vitro system to delineate mechanisms by which ammonia contributes to the development of AT2A. We found increased levels of GMF, aggregated protein lattice α/α, and inflammatory factors (IL-1β, TNF-α, IL-6, CXCL1, MMP-3, PG2 and COX2), as well as reduced levels and oxidized forms of α-tubulin in astrocytes post-ammonia treatment, which was similar to that found in vivo. Further, exposure of cultured neurons to conditioned media (CM) from ammonia-treated astrocytes (AT2A), but not ammonia per se, resulted in reduced levels of neuronal PSD95, synaptophysin and NMDA-m, as well as reduced synaptic density and dendritic complexity. Note-worthily, pharmacological inhibition of GMF, or silencing GMF by CRISPR reversed the defective neuronal integrity post-exposure of neurons to CM from ammonia-treated astrocytes in vitro.

CONCLUSIONS: These findings strongly suggest that increased levels of GMF post-CLF may negatively impact neuronal integrity that may ultimately contribute to the neurobehavioral/cognitive and motor deficits observed in CHE. We anticipate that our studies aimed at a better understanding of the molecular mechanisms involved in the development of AT2A, and its impact on neuronal integrity in CHE, will greatly facilitate the identification of agents capable of ameliorating this debilitating condition.
Obesity Accelerates and Exacerbates Neurological Impairments Associated to Hepatic Encephalopathy in Chronic Liver Disease

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BACKGROUND: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome observed in chronic liver disease (CLD/cirrhosis). With an increasing prevalence of obesity-induced cirrhosis and evidence linking blood-derived lipids to neurological impairment, we hypothesize that obesity increases the risk, severity and progression of HE.

AIM: Investigate the synergistic effect of obesity and CLD on the development of neurological impairment in a novel rat model of cirrhosis and obesity.

METHODS: Animal model of CLD and HE: 5-week bile-duct ligation (BDL) rats and Sham-operated controls, were used. Groups: Obese-BDL and Obese-Sham received high-fat diet (HFD) for 22-days pre-BDL and high-carbohydrate diet (HCD) for 5-weeks post-BDL; Lean-BDL and Lean-Sham received regular-diet (RD) pre-BDL and HCD post-BDL. Body-weight and fat-mass (EchoMRI) were monitored pre-BDL as well as 3- and 5-weeks post-BDL. Behavior: Motor-coordination, motor skill-learning, and muscular-strength were assessed at 3- and 5-weeks post-BDL. Locomotion and anxiety were measured at 3-weeks. Plasma ammonia, liver enzymes, and lipids were measured at 3- and 5-weeks.

RESULTS: Before BDL surgery, body-weight and fat-mass of rats on HFD increased compared to rats on RD. 5-week post-BDL, body-weight and fat-mass decreased in Lean-BDL and Obese-BDL vs respective Shams, while liver fibrosis (hydroxyproline content) was attenuated at 3, but not 5 weeks post-surgery. None of the circulating liver markers were changed by the treatments at any timepoint. Motor-coordination, muscle-strength, locomotion and anxiety were assessed in the 5-week BDL groups. RESULTS: Motor-coordination, muscle-strength, locomotion and anxiety were affected in all BDL groups without protective effect of treatments. Short-term memory (STM) was impaired in BDL-Veh (P < 0.001) and BDL-SYNARG (P < 0.05) versus Shams, while STM was restored in BDL-SYNARG+BUT (P < 0.05 vs BDL-Veh). Long-term memory (LTM) was impaired in BDL-Veh vs Shams (P < 0.05), but BDL-SYNARG and BDL-SYNARG+BUT were protected. CONCLUSIONS: EcN, engineered to consume ammonia in the gut and synthesize butyrate, is an effective approach to lower plasma ammonia in a model of cirrhosis and HE. Moreover, the attenuation of hyperammonemia in cirrhotic rats is associated with a protective effect on memory in this model. The therapeutic potential of these engineered EcN strains should be further evaluated in patients with CLD and HE.

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