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 (TLR9-9) 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 (dHR: 1.65 (1.82-22.9) 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 (dHR: 1.42 (1.2-14.3) P = 0.024; 10.9 (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.

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 571.5) on separate dates. We excluded patients with any decompensation event (defined by ICD codes,
Clinical Value of Asterixis in a Large Population of Well-characterised Patients With Cirrhosis and Varying Degree of Hepatic Encephalopathy

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BACKGROUND: Current guidelines for the diagnosis of overt hepatic encephalopathy (HE) include the clinical sign asterixis, which has also been used as an outcome in clinical trials. Limited information is available on the ability of physicians to detect/grade asterixis, and the relationship between asterixis and other HE indices. The aim of the study was to retrospectively assess the clinical value of asterixis in a large population of well-characterised patients with varying degree of HE.

METHODS: Asterixis was sought for in 374 consecutive patients with cirrhosis (57 ± 8 yrs, 280 males, MELD 14 ± 5, Pugh 7.9 ± 2.0) by trainees in Internal Medicine (n = 16), attending the Padova HE clinic between 2011 and 2019. Patients were asked to stretch their arms, extend their wrist and spread their fingers, and observed for 1 min. Asterixis was qualified as absent, rare, frequent or continuous. All underwent neuropsychiatric examination as per local protocols, including electroencephalography (EEG) and a set of neuropsychological tests (Animal Naming Test (ANT), Psychometric Hepatic Encephalopathy Score (PHES), computerised simple (sRT), choice (cRT) and Scan (Sc/ScRT) reaction times). Laboratory indices (venous ammonia, CRP, sodium) were recorded, together with previous 6 HE episodes and spontaneous surgical portal-systemic shunts. Patients were followed up for 24 months in relation to the development of HE-related hospitalisations. RESULTS: 280/59/33/2 patients were qualified as having no/rare/frequent/continuous asterixis, thus those with frequent and continuous asterixis were grouped for purposes of subsequent analyses. Associations were observed between the presence/degree of asterixis and the presence of overt HE on the day of study (χ² = 55, P < 0.001), a history of HE (χ² = 21, P < 0.001), and the presence of portal-systemic shunts (χ² = 11.8, P = 0.019). Significant differences in neuropsychiatric HE indices were observed between patients with different degrees of asterixis. Some were more prominent between patients without the sign, regardless of its frequency (PHES, ScanRT), while for others the relationship was linear (ANT, sRT, cRT, spectral EEG parameters). Significances in laboratory indices of liver failure/HE were also observed between patients with different degrees of asterixis. Again, some were prominent between patients without/with the sign (Pugh, CRP), while for others the relationship was linear (MELD, ammonia). Finally, the likelihood of developing HE-related hospitalisations over the follow-up period was significantly higher in patients with asterixis (Cox-Mantel P = 0.028).

CONCLUSIONS: Asterixis is reliably detectable/graded by specialist trainees in a tertiary referral liver centre, and shows significant associations with established neuropsychological, neuropsychiatric and laboratory HE indices, as well as the likelihood of developing HE-related hospitalisations over time.

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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 of CLD and HE and compare to male BDL rats.

METHODS: Female rats underwent either BDL (n = 8) or Sham (n = 8) surgery. After 5 weeks, assessed estrous cycle phase (by cellular cytology), anxiety (open field test), motor coordination (rota- rod test) and night-time activity. We also assessed body weight, body composition (MRI), gastrocnemius muscle circumference/weight and grip strength. BDL in female rats induced a dysregulated estrous cycle compared to Sham (increased metestrus phase (P < 0.05), decreased proestrus phase (P < 0.0001)). Similar to male BDL rats, female BDL rats had increased anxiety (P < 0.005), increased night-time activity (P < 0.05) and decreased day-time activity (P < 0.05) compared to female Sham. These results were comparable to male BDL rats except ALT and AST which were significantly higher in female BDL rats compared to male BDL rats.

CONCLUSIONS: We demonstrated that in female BDL rats, the main difficulty in using females is the impact of the estrous cycle, increasing intragroup variability. Interestingly, female BDL rats developed unique features. Contrary to male BDL vs. Sham, body weight and muscle mass does not differ between female BDL and Sham. 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 Sham) 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.
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. Neuroumolecular 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 immunohourting, immunohistostaining and/or qPCR. Microglia were stained by IBA1 and cortex field staining and cell morphology were assessed. In vitro, mouse neurons were transfected with a Let7f mimic and treated with vehicle or rIGF1 for 4 to 24 hr. The expression and secretion of IGF1 and the proinflammatory chemokine, CCL2, was assessed by qPCR and EIA.

RESULTS: Mice injected with AOM had increased Let7f and decreased IGF1 expression in the frontal cortex. Treatment with a Let7f antagonist attenuated the i) suppression of cortical IGF1, ii) neuroinflammation, 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 dampened IGF1 signaling attenuated the neurological and neuromuscular deficits, as well as the neuroinflammation 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, visuospatial & 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: 169 cirrhotics and 108 non-cirrhotic subjects were included. Demographics/education levels were statistically similar between centers. Controls were older than cirrhotics (74.9 ± 6.6 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 Off + On = 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 3.3 ± 8.4 vs 7.2 ± 11.1, Phys 3.0 ± 6.2 vs 6.7 ± 9.5, all P < 0.001). Within cirrhosis 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% (17 / 101) 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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Assessment of Cirrhotic Patients With Covert Hepatic Encephalopathy (HE) Through the EncephApp (Stroop-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 EncephApp (Stroop-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 EncephApp in the German population.

METHODS: 81 patients with liver cirrhosis underwent the testing of the CFF, the PHES-Test and the EncephApp. 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 Ons-plus-Off Time of the EncephApp was compared to the results of the CFF and the PHES-Test. Different Cut-Offs of the Ons-plus-Off Time were analyzed. Within these HE groups, the mean values of the PHES-Test, the CFF and the Ons-plus-Off Time of the EncephApp 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 EncephApp, 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 >724 sec with the most specificity with better sensitivity (82%). Other Cut-Offs 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 Ons-plus-Off Time in the EncephApp is >224 sec. In comparison with the CFF and the PHES-Test, most of the patients registered in higher grade HE would be detected by the EncephApp. The EncephApp is a valid and quick method to diagnose minimal HE but it has its limitations in the grading between HE grade 1 and 2.
analyzed cognition (EncephalApp higher = 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. Correlation network complexity was compared between post-FMT vs post-placebo states.

**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 engraftment of donor microbiota with higher Ruminococcaceae & Lachnospiraceae in stool/duodenum (Figure 1b,d). BA ratios: 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 |
|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| T2                                              | Healthy controls | HE (n=55) | HE (n=55) | NHE (n=55) | NHE (n=55) | p value |
| PHES (25th; 75th Percentile)                    | 1 (2.2)          | 0 (-2.1) | 0 (-2.1) | 0.5 (-1.2) | 0.5 (-1.2) | <0.01* HE vs Con <0.01 |
| RBANS T5 (meansSD)                              | 99.9 ±12.0       | 99.5 ±15.6 | 94.4 ±12.5 | 94.4 ±12.5 | 94.4 ±12.5 | <0.01* HE vs Con: 0.001 |
| RBANS Sumscore (meansSD)                        | 500.9 ±39.9      | 483.5 ±57.2 | 480.8 ±45.9 | 480.8 ±45.9 | 480.8 ±45.9 | 0.001* HE vs Con: 0.001 |
| RBANS Attention (25th; 75th Percentile)         | 103 (94/112)     | 98.5 (79/103) | 98.5 (79/103) | 98.5 (79/103) | 98.5 (79/103) | 0.001* HE vs Con: 0.001 |
| RBANS Delayed Memory (25th; 75th Percentile)    | 99 (94/106)      | 96 (91/104.5) | 97.5 (94/102) | 97.5 (94/102) | 97.5 (94/102) | 0.41 |
| RBANS Visuospatial/Constructional (25th; 75th Percentile) | 89 (81/105) | 84 (73.5/102) | 85.5 (77.3/102) | 85.5 (77.3/102) | 85.5 (77.3/102) | 0.42 |
| RBANS Immediate Memory (25th; 75th Percentile)  | 108 (94/112)     | 88.5 (81.5/106) | 95.5 (86/109.8) | 95.5 (86/109.8) | 95.5 (86/109.8) | 0.001* HE vs Con: 0.001 |
| RBANS Language (25th; 75th Percentile)          | 101 (96/106)     | 101 (87.3/106) | 99 (93.5/110.5) | 99 (93.5/110.5) | 99 (93.5/110.5) | 0.04 |
| CFF (25th; 75th Percentile)                     | 44.4 (41.8/46.5) | 42.7 (39.8/44.35) | 42.4 (41.3/46.5) | 42.4 (41.3/46.5) | 42.4 (41.3/46.5) | 0.04* HE vs Con: 0.04 |
| ICT Targets (%) (25th; 75th Percentile)         | 68.5 (96/79.5)   | 97 (92.99) | 97 (96.99) | 97 (96.99) | 97 (96.99) | 0.03* HE vs Con: 0.03 |
| T3                                              | Healthy controls | HE (n=46) | HE (n=46) | NHE (n=46) | NHE (n=46) | p value |
| PHES (25th; 75th Percentile)                    | 2 (0.3)          | 1 (-1.2) | 1 (-1.2) | 1 (-1.2) | 1 (-1.2) | 0.42 |
| RBANS T5 (meansSD)                              | 100.5 ±12.5      | 98.5 ±12.4 | 101.1 ±15.6 | 101.1 ±15.6 | 101.1 ±15.6 | 0.69 |
| RBANS Sumscore (meansSD)                        | 500.4 ±41.2      | 495.5 ±44.6 | 504.1 ±57.2 | 504.1 ±57.2 | 504.1 ±57.2 | 0.73 |
**The Role of Monocarboxylate Transporter-1 and Lactate Metabolism on the Development of Cognitive Deficits During NAFLD**

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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, monocarboxylate 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 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 neuropathophysiological alterations in NAFLD.

**P: 13 Junior Investigator | Oral Presentation**

The Role of Monocarboxylate Transporter-1 and Lactate Metabolism on the Development of Cognitive Deficits During NAFLD

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

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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. Down-regulation 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 computerised psychometric testing, WTAR and SF6 scores. Color-naming subset of the Stroop task was significantly impaired at baseline in LOLA recipients ($P = 0.0179$) 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 baseline 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

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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 (TDLD), 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 (PHES), Montreal Cognitive Assessment (MOCA), liver failure 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, 52 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 ($P = 0.73$), PHES ($P = 0.97$), 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 PHES ($P = 0.57$) 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.

P: 15  Junior Investigator | Oral Presentation

Functional MRI: Evidence of a Treatment Effect of LOLA

Yasmin Pasha, MBBS, MRCP,1 Sebastian A. Atzori, MBBS,1 Julie A. Fitzpatrick, Nicola A. Cook,2 Adrian Schenbri, PhD3, Robert Leech, PhD4,5, Mark J. W. Mephaïl, MBBS, MRCP, PhD5.

1Imperial College London, UK; 2Kings College, London, UK; 3RMIT University, Melbourne, Australia; 5QIMR, Brisbane, QLD, Australia.

BACKGROUND: Minimal hepatic encephalopathy (MHE) is associated with structural and functional connectivity abnormalities in the brain which correlate with cognitive dysfunction. The default mode network (DMN) comprises functionally interconnected brain regions responsible for attention and may explain cognitive deficits in MHE. While L-ornithine L-aspartate (LOLA) may improve MHE, its mechanism of action is not well characterised in controlled studies.

METHODS: We performed a double-blind, randomised trial comparing the impact of oral L-ornithine L-aspartate (LOLA) 6g three times per day with placebo on 34 individuals with MHE (defined by PHES) for 12 weeks. Fourteen subjects received LOLA. 20 patients received placebo for the study duration. Subjects underwent functional MRI (fMRI) of the brain while performing motor and cognitive tasks and resting state studies at baseline (before starting on LOLA) or placebo, and at 12 weeks. The motor and cognitive task data in the LOLA arm (vs placebo) were analysed by comparing the sum total of fMRI activation at baseline with data collected at 12 weeks. For resting state data, the level of functional connectivity within a network was compared between baseline and 12 weeks for LOLA against placebo.

Figure 1 Change in mean venous ammonia in FMT and placebo groups comparing baseline to day 7 and baseline to day 30

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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 (p < 0.05). The Stroop test had the highest sensitivity 70% [CI 47%–86%] whilst the CFF had the highest specificity 78% [CI 66%–87%] P 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 Hadjihambi, PhD1,2, Patrick S. Hosford, PhD1, Abeba Habetion2, Nathan Davies, PhD2, Alejandro V. Guariné, PhD2, Rajan Jalan, PhD, MD2.
1Univrsité de Lausanne, Department of Physiology, Lausanne, Switzerland, 2ICL 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, Physiology and Pharmacology, University College London, 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.
EID-UL-AZHA (Muslim’s Festival of Sacrifice): Increased Frequency of Spontaneous Encephalopathy, Whether This Is Secondary to Consumption of High Protein Diet?
Rehmatullah Bhatti1, Abdu 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. Giannou, PhD1, Rehmatullah Bhatti1

1Asian Institute of Medical Sciences (AIMS), Hyderabad, Pakistan.

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. Patient 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 578 screened patients, 92 were presented with encephalopathy. All patients were Muslims with mean age 54.8± 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.

Changes in Cerebral Hemodynamic Parameters in Patients With Acute Liver Failure
Juanita Pérez, MD1, Viridiana López, MD1, Carlos Cantú, MD1, Fernando Flores, MD1, Aldo Torre, 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 loss of liver function in a patient without preexisting liver disease.1 High intracranial pressure (ICP) leads to loss of cerebral perfusion, brain herniation and irreversible brain damage in patients with acute liver failure.2–4 Objective: Compare the changes in cerebral hemodynamics, making it very useful in patients with ALF.

METHODS: Retrospective and descriptive study. We searched patients with ALF during the period 2013-19 and admitted in the ICU. Patients with preexisting neurological disease (CNS infection), hypertension, aortic stenosis, peripheral vascular disease, and patients who died within 24 h of admission were excluded. Patient 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.

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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 AIMs (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, MELD, and CTP 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 86 (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 induce 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%). 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 commonest cause, precipitating acute insult was SEPSIS. Others were drug induced liver injury (DILI), HEV acute hepatitis, HDV superinfection, HBV flare, alcohol binge drinking, surgery, acute PVT, Upper GI Bleed, and 20% were unknown. Hospital mortality was 49 (41.9%), 28 days 71 (60.7%) and 12 weeks mortality was 103 (88%). 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

El Heba Omar, PhD1,2, El Khiat Abdelaati2, Aitihya Mohamed2, Gamrani Halima2.

1Department of Translational and Precision Medicine, With Liver Cirrhosis
2Institute of Translational Sciences, Hyderabad, Pak.) from January 2018 to December 2018. We enrolled patients of ACLF as
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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 commonest cause, precipitating acute insult was SEPSIS. Others were drug induced liver injury (DILI), HEV acute hepatitis, HDV superinfection, HBV flare, alcohol binge drinking, surgery, acute PVT, Upper GI Bleed, and 20% were unknown. Hospital mortality was 49 (41.9%), 28 days 71 (60.7%) and 12 weeks mortality was 103 (88%). Organ failure, ACLF grade, encephalopathy, MELD score and AKI were found to be predictors of mortality of ACLF.

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

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1Department of Translational and Precision Medicine, With Liver Cirrhosis
2Institute of Translational Sciences, Hyderabad, Pak.) from January 2018 to December 2018. We enrolled patients of ACLF as
developed encephalopathy. The aim of our study was to determine cause, precipitating acute insult, organ failure, ACLF grade, MELD, and CTP 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 86 (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 induce 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%). 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.

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The Modification of Quantity and Quality of Muscle Mass Improves the Cognitive Impairment After TIPS
Stefania Gioia, MD1, Manuela Merli, MD1, Silvia Nardelli, MD1, Barbara Lattanzi, MD1, Lorenzo Bidola, MD2, Oliviero Riggi, MD2.
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BACKGROUND: Hepatic encephalopathy (HE) is the major complication of transjugular intrahepatic 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.

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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 NeuroPsi 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 vaso-reactivity 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 ± 1.8. 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 hemodynamic parameters assessed by transcranial Doppler, there were no significant differences between compensated and decompensated patients.

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Decreased Mean Kurtosis in the Putamen Is a Diagnostic Feature of Minimal Hepatic Encephalopathy in Patients With Cirrhosis
Takuro Sato, MD1. 2Inova Medical University, Mariskia, Inwine, Japan.
1Institute Of Medical Science And Nutrition, Mexico City, Mexico.

BACKGROUND: To prevent development of overt hepatic encephalopathy, early intervention for minimal hepatic encephalopathy (MHE) based on accurate diagnosis is essential. This study evaluated to investigate whether magnetic resonance diffusion kurtosis imaging (DKI) and diffusion tensor imaging (DTI) could detect brain microstructure abnormalities in MHE. The aim was to confirm whether brain microstructure abnormalities detected by magnetic resonance imaging were used as diagnosis of MHE.

METHODS: Thirty-two subjects were prospectively examined with a 3-T MR scanner. Tract-based spatial statistics and region of interest analyses of diffusion imaging were performed to compare mean kurtosis (MK), fractional anisotropy (FA), and mean diffusivity (MD) values between patients with/without minimal hepatic encephalopathy. Diagnostic performance for detection of MHE was assessed with the receiver operating characteristic analysis.

RESULTS: Ten subjects were diagnosed as MHE by neuropsychological testing. After exclusion of unsuitable subjects, we analyzed 9 subjects with MHE and 14 subjects without MHE. There were no significant differences in the sex, age, and etiology of liver cirrhosis (alcohol/HCV/NAFLD; 4/3/2 vs 7/3/4, P = 0.12), in the number of episodes of overt HE (P = 0.14) or the length of time after first overt HE episode (P = 0.79). The amelioration of muscle wasting and HE independent of liver function observed after TIPS supports the causal relationship between muscle wasting and HE.

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>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) (yes/no)</td>
<td>8/3 (72.7%) (27.3%)</td>
<td>2/14 (12.5%) (87.5%)</td>
</tr>
<tr>
<td>PHEs score</td>
<td>-4.8±2.1</td>
<td>-1.6±2</td>
</tr>
<tr>
<td>Overt HE (yes/no)</td>
<td>9/2</td>
<td>10/6</td>
</tr>
<tr>
<td>OHE in the first 3 months (N of episodes/patient)</td>
<td>0.9±1.04</td>
<td>0.6±0.5</td>
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<tr>
<td>OHE in the following months (N of episodes/patient)</td>
<td>1.4±1.04</td>
<td>0.06±0.3</td>
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<tr>
<td>Venous plasma Ammonia (µg/dl)</td>
<td>96±31.5</td>
<td>48.5±28.7</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>11.9±6.2</td>
<td>11.4±6.7</td>
</tr>
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</table>

Mean ± SD

[26]

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0.29, respectively) when compared with the non-MHE group (0.16, 0.21, and 0.32, respectively) \((P = 0.012, 0.002, \text{and } 0.0001, \text{respectively})\). In contrast, MD values in the basal ganglia showed no apparent differences between the groups. Subsequently, we performed ROC analysis on the sites where significant differences were found in the ROI analysis.

Among the metrics, MK values of the Put achieved AUROC of 0.90, and sensitivity, specificity, positive predictive value, and negative predictive value of more than 80% (0.89, 0.86, 0.88, and 0.92, respectively) between the MHE and non-MHE groups. In conclusion, mean kurtosis on the putamen was a useful finding to distinguish patients with MHE among subjects with liver cirrhosis.

CONCLUSIONS: DKI detects changes in the cerebral white matter and basal ganglia regions of the patients with MHE more sensitively than DTI. MK values in the putamen can be a useful marker for diagnosing MHE from cirrhotic patients without MHE.

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Contributors to Balance Impairment in Adults With Cirrhosis and Hepatic Encephalopathy

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

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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Relation Between Mortality and Psychometric Test Results in Patients Awaiting Liver Transplantation

Ann-Katrin Wirries\(^1\), Henning Pflugradt\(^2\), Anita Blaüke-Truy\(^1\), Hannes Borg-Hack\(^3\), Jürgen Klemmpanner\(^1\), Annenmarie Goldbeck\(^4\), Christian Strausberg\(^5\), Karin Weissenhorn\(^1\),

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BACKGROUND: Hepatic encephalopathy is a common severe complication of liver cirrhosis that, however, so far is not considered as an indication for organ allocation to patients on the transplant waiting list. Multiple psychometric tests have been developed to detect hepatic encephalopathy. However, there is only rare data about the predictive value of psychometric test results regarding mortality in patients with liver cirrhosis. This retrospective analysis of prospective data determined the predictive value of the Inhibitory Control Test (ICT), the Repeatable Battery for the Assessment...
of Neuropsychological Status (RBANS), the Postsystemic 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 Postsystemic 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 five-year survival rate was analyzed with the Kaplan-Meier curve.

RESULTS: Patients with abnormal PHES had a significantly higher mortality risk than patients with a normal PHES (P < 0.001). Also patients with an abnormal RBANS result had a significantly higher risk to die than patients with a normal RBANS result (P = 0.018), 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).

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

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The Natural History of Cirrhosis After the Development of Hepatic Encephalopathy
Jeremy Louisant1, MD, Elliot B. Tapper, MD2

1University of Michigan, Ann Arbor, MI, USA.

BACKGROUND: Hepatic encephalopathy (HE) is a watershed moment in the natural history of cirrhosis portending decreased quality of life and worsening prognosis. Recent strides in the management of HE have been made to decrease symptom burden and readmissions. The impact of these interventions requires a contemporary re-examination of the natural history of HE and its clinical implications.

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 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 1.02–1.03), male sex (HR 1.21, CI 1.19–1.24), ESRD (HR 1.08, CI 1.01–1.14), and increasing Charlson Comorbidity Index (HR 1.2, 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 0.82 CI: 0.79–0.85, respectively) while NAFLD was linked to increased mortality after HE (HR 1.42, CI: 1.17–1.48). 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 (IRR 0.35, CI: 0.33–0.37) 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.

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.

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Liver Transplant Is Associated With Improvement in Cognition, Tandem Gait and Risk of Falls
Chathur Acharya, MD1, Melanie B. White, RN1, Andrew Fagan2, Richard K. Sterling, MD1, R. Todd Stravitz, MD2, Punam Puri, MD1, Michael Fuchs, MD1, Yelimir Luketic, MD1
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, 3 quantification with LCM0 model) 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 osmolytes (Inositol, Taurine, Creatine 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 osmolytes than hippocampus (Figure 1d,e). 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 neuro-metabolism in 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.

REFERENCES

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WITHDRAWN

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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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1UCL Medical School, London, UK; 2Royal Free Hospital, London, UK; 3All India Institute of Medical Sciences, New Delhi, India.

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 these 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.

METHODS: Cirrhosis is associated with poor health related quality of life (HRQOL), cognitive and physical frailty (CF/PPF), that manifest as overt/ 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, 37 (61%) had CHE, 20 (32.7%) with CHE and brain.1 The evidence that ammonia uptake 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: 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. Cox-proportional hazard analysis was used to assess predictors of infection.

RESULTS: 759 cirrhotic patients with AD were included with a median age of 45 years, and varying degrees of HE; grade 0/1 (n = 452), grade 2–4 (n = 307). On day 0, Patients classified into 4 groups; no HE no infection (n = 359), overt HE no infection (n = 222), no HE with infection (n = 93), overt HE with infection (n = 83). OFs (Liver, Renal, Brain, Coagulation, Respiratory, and Circulatory) and ACLF grades were measured on Day 0; with ACLF grade 0, 1, 2, and 3 (n = 242, 99, 206, and 212 respectively). On univariate and multivariate analyses, Overt HE (with no baseline infection) was independently predictive of new infections (1.639 and 1.608; P < 0.001, and 0.017 respectively). Furthermore, age and circulatory failure were also independent risk factors for infections. That would make them, after further studies, an indication for prophylactic antibiotics.

CONCLUSIONS: 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.

REFERENCES

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Junior Investigator

Antibiotic Rifaximin for Treatment of Chronic Liver Disease-Induced HE: A Longitudinal In Vivo 1H-MRS Study of Brain Metabolism on BDL Rats

Emmanuelle Flatt1,2, Olivier Braissant2, Stefania Mittova2,4, Dario Salvi2, Rolf Grutter1,2, Valerie A. McLin5, Cristina Cadabu2,4
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BACKGROUND: Rifaximin is a commonly-used antibiotic to treat hepatic encephalopathy (HE), a complex neuropsychiatric syndrome caused by hepatic dysfunction. Rifaximin aims at reducing the production of gut ammonia, an important toxin in HE pathogenesis. In a previous study using bile duct ligated (BDL) rats, we showed that rifaximin at the recommended human dose may help reduce brain Gln levels in early stages of HE.3 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).5

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 = 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.4

RESULTS: Plasma measurements of bilirubin confirmed the presence of CLD in all groups of rats. They displayed similar ammonium concentration across groups (Figure 1a). ISHEN treated rats revealed some significant differences between the high-dose rifaximin group and 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, creatine, 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.3,6
**P: 37  Junior Investigator**

**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 BDL1,2 (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 (2.8 × 2.8 × 2 mm³) and cerebellum (2.5 × 2.5 × 2.5 mm³). Metabolite concentrations were estimated using LCModel and water as internal reference. Probiotics administration (LIVOMEXX, 60 billion bacteria/kg of rat) started two weeks before BDL-surgery until the end of the study. Rifaximin (15.7 mg/kg/day) was administered twice daily starting two weeks after BDL-surgery.

**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. The combination of probiotics and rifaximin improved some of the neuro-metabolic changes associated with CLD at early stages of HE (week 4) in the cerebellum: the ‘probiotics + rifaximin’ group showed a lower increase of brain glutamine (+13% vs +66%, Figure 1c) and a smaller decrease of creatine (–4% vs –14%). In the hippocampus, rats receiving both probiotics and rifaximin exhibited a smaller increase in brain glutamine 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 –33%, 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**

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**P: 38  Junior Investigator**

**Rifaximin Reduces the Incidence of Spontaneous Bacterial Peritonitis, Variceal Bleeding and All-cause Admissions in Patients on the Liver Transplant Waiting List**

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**BACKGROUND:** Rifaximin reduces the risk of overt hepatic encephalopathy (HE) in patients with advanced chronic liver disease (ACLD) and is associated with significant reductions in hospitalisations and 30-day readmissions. This study examined clinical outcomes of patients listed for liver transplantation with a diagnosis of HE on rifaximin compared to those naïve to the drug.

**METHODS:** Patient records of those listed for liver transplantation over a 2-year period were retrospectively reviewed. Patients were included if they had at least two episodes of overt HE resulting in hospitalisation or were encephalopathic at the time of assessment. Information collected included patient demographics, aetiology of liver disease, disease severity scoring at transplant listing, concomitant medications and medical co-morbidities. Emergency admissions whilst on the waiting list for complications of ACLD in addition to requirement for prioritisation (UKELD score ≥63), duration on the waiting list (days) and mortality on the waiting list were recorded. Univariate and multivariate regression analyses were performed on acute admission and complication data (related to sepsis, acute variceal bleeding (AVB), HE and complications of ascites) with rifaximin use as the independent variable.

**RESULTS:** Of the 622 patients listed for transplantation, 101 were listed with HE. 66 patients were treated with rifaximin and 35 were naïve at listing. Median MELD score was similar (15 [14–16] vs 16 [14–18] for rifaximin-naïve). The use of lactulose was not significantly different between groups. Patients on the waiting list treated with rifaximin had an independent association with reduced all-cause admissions (P = 0.037), episodes of spontaneous bacterial peritonitis (P = 0.008) and AVB (P = 0.026). Mean length of hospital stay was 9 (95% CI 6–12) in the rifaximin-treated group vs 14 days (95% CI 7–21) in the rifaximin-naïve group. Multivariate regression analysis demonstrated that rifaximin was independently associated with an increase in days to readmission.
Clinical outcomes from univariate and multivariate analyses comparing rifaximin-treated and rifaximin-naive patients on the liver transplant waiting list.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Univariate analysis [unadjusted effect estimate (95% CI), p value]</th>
<th>Multivariate analysis [confounder-adjusted effect estimate (95% CI), p value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause admissions/year</td>
<td>-3.55 [-6.55 to -0.55], p = 0.021</td>
<td>-3.10 [-6.00 to -0.20], p = 0.037</td>
</tr>
<tr>
<td>Days to readmission</td>
<td>+82 [48 to 117], p = 0.025</td>
<td>+71 [3 to 139], p = 0.040</td>
</tr>
<tr>
<td>Admissions with sepsis/year</td>
<td>-0.97 [-2.27 to 0.33], p = ns</td>
<td>-0.49 [-1.75 to 0.98], p = ns</td>
</tr>
<tr>
<td>Admissions with complications of ascites including SBP/year</td>
<td>-1.70 [-3.00 to -0.4], p = 0.010</td>
<td>-1.77 [-3.07 to -0.47], p = 0.008</td>
</tr>
<tr>
<td>Admissions with acute variceal bleeding/year</td>
<td>-0.89 [-1.59 to -0.19], p = 0.014</td>
<td>-0.81 [-1.52 to -0.10], p = 0.026</td>
</tr>
<tr>
<td>Admissions with overt hepatic encephalopathy/year</td>
<td>-0.01 [-0.81 to 0.79], p = ns</td>
<td>-0.07 [-0.95 to 0.81], p = ns</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>-5.74 [-12.5 to 1.06], p = ns</td>
<td>-6.35 [-12.85 to 0.15], p = ns</td>
</tr>
<tr>
<td>Intensive care admissions/year</td>
<td>-0.46 [-1.66 to 0.74], p = ns</td>
<td>-0.04 [-1.18 to 1.10], p = ns</td>
</tr>
<tr>
<td>Length of intensive care stay (days)</td>
<td>-1.40 [-3.80 to 1.20], p = ns</td>
<td>-1.15 [-3.65 to 1.10], p = ns</td>
</tr>
<tr>
<td>Requirement for prioritisation on the waiting list (odds ratio)</td>
<td>0.34 [0.0 to 0.72], p = 0.030</td>
<td>0.29 [0.0 to 0.71], p = 0.037</td>
</tr>
<tr>
<td>Mortality on the waiting list (odds ratio)</td>
<td>0.66 [0.0 to 1.61], p = ns</td>
<td>0.40 [0.0 to 1.09], p = ns</td>
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</tbody>
</table>

P: 39 Junior Investigator

Modulation of the Urea Cycle Function by Toll-like Receptor 4 Signaling: A Potential Novel Therapeutic Target for Hyperammonemia and Hepatic Encephalopathy

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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 (WT, n = 7), WT with HA (WT+H, 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 carbonamyl phosphate synthase type 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 more effective than LPS alone.

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CONCLUSIONS: compared to WT mice, as shown by both Western Blot and immunohistochemistry.

of UCEs between groups, protein expression of CPS1 was signi

cificance decreases gene expression, synthesis of proteins, and growth

decreased, whereas protein expressions of albumin, the urea cycle enzymes, and glutamine synthetase

were normal. However, 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.

METHODS: Female Wistar rats were fed a K1-free diet for 13 days. Half of the rats were then repleted with K1 for one week following depletion. K1-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 liver tissue potassium concentrations were decreased, but unchanged in the liver tissue. Gene expression of albumin and two out of five urea cycle enzymes were moderately decreased, whereas protein expressions of albumin, the urea cycle enzymes, and glutamine synthetase were normal. However, 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.

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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 K1-free diet for 13 days. Half of the rats were then repleted with K1 for one week following depletion. K1-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 liver tissue potassium concentrations were decreased, but unchanged in the liver tissue. Gene expression of albumin and two out of five urea cycle enzymes were moderately decreased, whereas protein expressions of albumin, the urea cycle enzymes, and glutamine synthetase were normal. However, 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.

REFERENCES

1. Faust F, Schubbert S. Protein synthesis is the most sensitive process when potassium is substituted by sodium in the nutrition of sugar beet (Beta vulgaris). Plant physiology and biochemistry: PPR 2016;107:237–247. doi:10.1016/j.plaphy.2016.06.009.

P: 41 Junior Investigator

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 morbidity in patients with liver disease. Common culprits include gastrointestinal bleeding, infection, constipation, hypokalemia, hyponatremia, and medications such as opiates and benzodiazepines. This study aim 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%
To Assess Frequency of Hepatic Encephalopathy in Spontaneous Bacterial Peritonitis Patients

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1. Asian Institute of Medical Sciences, Hydrobad, Pakistan.

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.

METHODS: This cross-sectional study was conducted at the Gastro-heptology 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 etiology was HCV (41.7%). 23 were CTP P1 (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 HE in all patients with SBP should be considered and over-the-counter PPI use should be restricted.

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 liver failure. However, none of the current methods for evaluating brain water content fulfills the ideal requirements of a measuring technique, being complex, expensive, lengthy, qualitative or insensitive. Our aim was to evaluate a novel protocol for measuring brain water content using a moisture analyzer in a rodent model of hyponatremia-induced brain edema.

METHODS: Female Sprague-Dawley rats (248 ± 41 g bw) undergoing a 3-hour protocol for inducing hyponatremia-related brain edema (HypoNa group) were compared with a group of normonatremic rats (Control group). All rats were anesthetized with sevoflurane and mechanically ventilated. Body temperature was maintained at 37 ± 0.5°C using warm air. Plasma water content was measured in the normonatremic (Control) and hyponatremic (HypoNa) groups at baseline, 1, 2, 4, 6, 8, 12, and 24 hours after i.p. injection of LPS to induce ACLF. Brain tissue was dissected and placed in a moisture analyzer (Mettler Toledo MB120, Ohaus Corporation) between two glass fiber filters for measuring brain water content by the wet-to-dry weight method. Dry weight (g) was determined when there was no change in 1 mg for 5 minutes.

RESULTS: Compared with the Control group, rats in the HypoNa group presented lower sodium (334 ± 10.8 vs. 164.8 ± 10 mmol/L, P < 0.001), potassium (1.27 ± 0.04 vs. 1.15 ± 0.03 mmol/L, P < 0.05), and effective osmolality (281 ± 2.1 vs. 228.8 ± 3.8 mOsm/L, P < 0.001), and a trend to increased concentrations of potassium (410 ± 15 vs. 475 ± 40 mmol/L, P = 0.25) and lactate (2.23 ± 0.38 vs. 2.23 ± 0.18 mmol/L, P = 0.22) in plasma. Frontal cortex water content was higher in the HypoNa group (Control: 82.20 ± 0.74 vs. HypoNa: 85.01 ± 0.97 ‰, P < 0.01). Measuring time of water content using the moisture analyzer was ≤15 minutes per sample.

CONCLUSIONS: These results suggest that the present protocol using a moisture analyzer is a convenient and sensitive method for measuring brain water content in rats.

Ammonia Is an Independent Biomarker of Poor Outcomes in Patients With Advanced Cirrhosis

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BACKGROUND: Ammonia plays a pivotal role in the development of hepatic encephalopathy (HE) and brain oedema in acute liver failure and is a prognostic biomarker. However, its utility as
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 (ammonia measured at the time of assessment for transplant. All patients were closely followed up until death or 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 5 (1.8%) were still active 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 = 0.00135). 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). In this retrospective study, arterial ammonia at the time of listing for liver transplantation was an independent predictor of hospitalisation, 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. Fourteen patients (12.4 %) died during the study period due to complications of liver cirrhosis other than HE. For 67 subjects follow-up data was 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
Figure 1. Cumulative incidence of HE-related readmissions

[48]

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 (SSBB) 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 SSBBs. In multivariate analysis, after adjusting for age, sex, MELD score, SSBB 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.

P: 49 Junior Investigator

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

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1Virginia Commonwealth University, Richmond, VA, USA; 2McGuire VAMC, Richmond, VA, USA.

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 MRI & free of alcohol/drug use. Cirrhotics 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 curved 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 gyri) 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.

P: 50 Junior Investigator

Developing a New Animal Model of Episodic Hepatic Encephalopathy

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1Virginia Commonwealth University, Richmond, VA, USA; 2McGuire VAMC, Richmond, VA, USA.

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 MRI & free of alcohol/drug use. Cirrhotics 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 curved 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 gyri) 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.
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). Saline was injected as vehicle for non-episodic groups. Two days following the last HE episode, we assessed motor-coordination (Rotadot), anxiety (elevated plus maze, EPM), 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 = 0.05) were exclusively found in episodic BDL rats compared to non-episodic BDL rats. Moreover, there was an increase in blood ammonia (P < 0.04), 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 remains 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, 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/AASLD 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 utility of aminoglycosides and metronidazole vs. placebo, non-absorbable disaccharides (NAD) and other active treatment, for the management of HE in adults with cirrhosis.

METHODS: Electronic/manual searches of the literature were undertaken for relevant RCTs. The evidence using GRADE.

RESULTS: 20 RCTs evaluated aminoglycosides including neomycin (n = 7), other antibiotics viz. rifaximin, erythromycin and ciproxin (n = 7). Aminoglycosides and other interventions, in relation to death and HE, in patients with cirrhosis, their use be used routinely in this setting.

CONCLUSIONS: Amoxicillin and Metronidazole for the Prevention and Treatment of 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 under-went 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 between 3 months of the neuro-cognitive 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 ± 9.6 yrs and 73% were males. Median Child Pugh score was 8 (IQR 6-10) and MELD was 12 (IQR 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 = 0.51), but not with sarcopenia or degree of hepatic dysfunction. Correlation between total effective shunt size and PHES was more pronounced in women (r = -0.68). Upon multivariate analysis, none of these variables predicted PHES. EEG mean dominant frequency correlated significantly with total effective shunt size (r = 0.38), 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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1Virginia Commonwealth University, Richmond, VA, USA, 2McGill VAMC Richmond, VA, USA.
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 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 hypothyroidism, 2% had CHF, 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 (2, 7) 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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Deceased Cognitive Performance Is Associated With Reduced Resting State Connectivity and Gray Matter Atrophy in Patients With Minimal Hepatic Encephalopathy

Raquel Garcia-Garcia, PhD1, Juan José Galligo2, Carla Giménez-García, PhD1,2, Natalia Varallo-Andreí2, Andrea Cabrera-Pastor2, Alvaro Javier Cruz-Gómez, PhD3, María Pilar Balbester, MD5, Alba Mangas-Losada, PhD5, Amparo Urus, PhD3, Cristina Forn, PhD5.
CONCLUSIONS: Decreased cognitive performance is associated by 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, PROMETEU/2018/051 to VF), CM, ACIF/2018/284 to JG, co-funded with European Regional Development Funds (ERDF).

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Evaluation of Cognitive Dysfunction in Animal Models and Relatability to Human Disease
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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 human disease.

Figure 1. Visual vs. spectral analysis of the EEG in HE
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 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.

Thrombospondin-1 Worsens Azoxymethane-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 TGFβ1 drives HE progression. Thrombospondin-1 (TSP-1) can activate latent TGFβ1 and therefore, we hypothesize that hepatic-derived TGFβ1 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 reflex and ataxia measurement. Liver histology was assessed by hematoxylin and eosin staining and serum transaminases were measured. Cleared capsaicin-induced 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. TGFβ1 and TSP-1 expression were assessed in liver, serum and cortex by immunoblotting, immunohistochemistry and real-time PCR. Cerebral edema and microglia activation were assessed and neuroinflammation 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 TGFβ1 and TSP-1 levels, with the cortex only having elevated TGFβ1. LSKL-treated mice and TSP-1 knockout mice administered AOM had reduced activation of hepatic TGFβ1, 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 TGFβ1 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: TGFβ1 and TSP-1 were elevated in the livers and serum of AOM-treated mice and strategies employed to reduce TSP-1 signaling reduced liver damage and neuroinflammation in the AOM mouse model of HE. Therefore, targeting TSP-1 signaling may be a novel therapeutic target for the management of both ALF and HE following acute liver injury.

Prediction of Overt Hepatic Encephalopathy by the Continuous Reaction Time Method and the Postoperative Encephalopathy Syndrome Test in Patients With Cirrhosis

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Table 1: T tests comparing non-cognitive covariates between groups positive and negative for CHE on PHES and Encephalapp stroop and multivariable logistic regression.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>CHE on PHES</th>
<th>CHE on Encephalapp Stroop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Yes (109)</td>
<td>No (148)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
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<tr>
<td>Male Sex</td>
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<td>BMI</td>
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<tr>
<td>Liver Disease Severity</td>
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<td>MELD</td>
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<tr>
<td>Child score</td>
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</tr>
<tr>
<td>CCI</td>
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</tr>
<tr>
<td>Prior OHE</td>
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<td>0.00</td>
</tr>
<tr>
<td>Ascites</td>
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<td>0.00</td>
</tr>
<tr>
<td>Prior variance bleed</td>
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Mortality:

<table>
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<th>Variable</th>
<th>CHE on PHES OR</th>
<th>CHE on Encephalapp Stroop OR</th>
<th>CHE on PHES P value</th>
<th>CHE on Encephalapp Stroop P value</th>
</tr>
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<tbody>
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<td>Age</td>
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<tr>
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</tr>
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</table>

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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: Participants with minimal HE (MHE) were randomised in a 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 55.8 ± 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% 3-3-dithionoylacryl-1,4-dihydrocollidine and 10% ammonium acetate (DDC + NH4). Neurobehavioral indices and neuropeptidic deficits were assessed by open field test, rotarod, grip strength test and gait analysis. Serum, liver and brain tissue were collected after 13 days of DDC + NH4 feeding. Liver damage was assessed by serum chemistry and H&E staining. Serum and cortical ammonia and total bile acid content were assessed with colorimetric assays. Cerebral edema was assessed using the wet weight/dry weight method. Microglia activation was assessed by Iba1 immunohistochemistry. The expression of proinflammatory cytokines were assessed by qPCR and ELISA.

Results: DDC + NH4 feeding caused significant neurological and neuropeptidic deficits in every test performed commencing after 5–7 days of feeding. The liver damage observed was like a cholestatic condition.

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%.
A selective ablation of FXR expression in the brain facilitates the development of HE. The role of FXR-mediated bile acid signaling in the pathogenesis of HE due to chronic liver cirrhosis is still unclear. We have previously demonstrated that abnormally high bile acid signaling via activation of 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.

**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-knockout mice were generated by crossing floxed FXR mice (FXRfl) with SNAP-25 cre recombinase mice. The resulting mice were designated FXRfl/cre (FXRfl). FXRfl and FXRfl/cre were treated with carbon tetrachloride (CCL4; 1 ml/kg) by oral gavage twice per week for 12 weeks. Neurobehavioural indices and neuromuscular deficits 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 assayed in the cortex and cerebellum using colorimetric assays. The expression of ASBT, FXR, and its downstream effector SHP was assayed by qPCR and immunofluorescence. The expression of proinflammatory cytokines (IL-1β, TNF-α) was assayed by qPCR and IHC. The expression of proinflammatory cytokines was assessed by qPCR and IHC. The expression of proinflammatory cytokines was assessed by qPCR and IHC. 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a 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).

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Animal Naming Test Is Highly Accurate and Reliable for Diagnosis of Minimal Hepatic Encephalopathy in Outpatients With Cirrhosis
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BACKGROUND: Background and Aims Minimal hepatic encephalopathy (MHE) is the mildest form in the spectrum of hepatic encephalopathy that impairs health-related quality of life. PHES remains the gold standard for the diagnosis of this condition. Animal naming test (ANT) is reliable and sensitive tool for diagnosis of MHE and can also predict overt episodes of HE. We compared usefulness of PHES and ANT for the diagnosis of MHE and for the prediction of the development of overt episodes of HE.

METHODS: Between July 2017 to June 2018, one hundred and three consecutive patients with liver cirrhosis without overt HE were subjected to PHES and ANT evaluation. MHE was diagnosed when the PHES was ≤ 5. Receiver-operating characteristic (ROC) curve was used to determine the optimum cut-off of ANT value for the diagnosis of MHE. The best specificity and sensitivity was found at <14. Patients were followed up every 3-6 months till October 2018.

RESULTS: Thirty-seven (35.9%) patients had MHE as assessed by altered PHES. ANT (<14) was present in 36 (34.95%) patients with MHE with sensitivity of 89.19% and specificity of 95.7%, PPV of 91.67%, NPV of 94.03% and diagnostic accuracy of 93.20%. The area under the curve for diagnosis of MHE was 0.978 (95 CI 0.954-1.0). MHE patients had significantly lower ANT as compared to non MHE patients and controls (10.81 ± 0.32 vs 15.27 ± 0.14 vs 15.78 ± 0.19, respectively, P < 0.001).

MHE patients had lower hand grip strength compared to non-MHE patients and the control group (Males: 26 vs 30 vs 38, Females 25 vs 28 vs 28, P < 0.05). PHES significantly correlated with Child-Pugh (r = -0.421, P = 0.001) and model for end-stage liver disease (MELD) (r = -0.417, P = 0.001) scores. ANT correlated with PHES (r = 0.752, P = 0.001) and also with Child-Pugh (r = -0.408, P = 0.001) and MELD (r = -0.318, P = 0.001) scores. During follow-up, 14 patients in MHE group and in non-MHE group developed overt episodes of HE (P = 0.001). Out of 37 patients with abnormal PHES 14 patients developed overt HE on follow up and out of 36 patients with abnormal ANT 14 patients developed overt HE on follow up. 33 patients had both PHES and ANT abnormal. 4 patients had PHES abnormal and ANT normal. 3 patients had PHES normal and ANT abnormal.

CONCLUSIONS: ANT is a highly accurate and reliable test for the diagnosis of MHE and prediction of overt episodes of HE in outpatients of cirrhosis as compared to PHES and correlates well with the Child-Pugh and MELD scores.

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Drug-induced Hyperammonemia: 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 hyper-ammonemia is most commonly secondary to liver diseases, portosystemic shunts, inborn errors of metabolism, most often are cycle defects, microbial pillulation or drug-induced hyperammonemia (DIH) are other possible causes. DIH is poorly described but is mainly recognized as the consequence of valproic acid. Some antineoplastic agents, fluoroacil or asparaginase, have been implicated but this class is evolving rapidly. To describe the drugs associated with DIH.

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 (MedDRA)v21.1 term (Preferred term [PT] level). The drugs considered in the analysis were those notified as suspected treatments. Drugs used to treat hyper-ammonemia or hepatic encephalopathy 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 (IC[0.25]) > 6, 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 hyperammonemia or hepatic encephalopathy. Thus, 73 drugs had an IC[0.25] > 6 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 associated in DIH. These data could help in the etiological work-up of hyperammonemia.

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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 reported 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 ICU. Plasma samples from cirrhotic patients displaying encephalopathy were compared to plasma from cirrhotic patients without neurological symptoms, and to plasma from healthy controls. Liquid chromatography coupled to high-resolution mass spectrometry was performed and thenafter the metabolic profile was compared to plasma from healthy controls. Liquid chromatography coupled to high-resolution mass spectrometry was performed and thenafter the metabolic profile was compared to plasma from healthy controls.

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], MELD 17 [14–29], alcohol 38%) and 9 healthy controls. Among 495 identified metabolites,
25 corresponded to xenobiotics or its derivatives. Fluoxetine was detected with a more than 300 fold increase, ascorbic acid with a more than 10 fold increase and benzyl alcohol (present in cough pills and antiseptics) with a 3 fold increase in cirrhotic patients with encephalopathy as compared to cirrhotic patients. In cirrhotic patients with or without encephalopathy, propranolol was detected with a more than 8500 fold increase, acetaminophen with a 40 fold increase, penicillin and ampicillin both with a 2 fold increase as compared to healthy controls. Interestingly, several substances which were not expected to have systemic diffusion were detected in cirrhotic patients and in healthy controls: eugonol, isoegonol (used in mouth bathing solution), triethanolamine (tolramin, used in cutaneous creams) and resorcinol monoacetate (used in mouth bathing solution and in cutaneous creams).

CONCLUSION: Cirrhotic patients, especially those with neurological symptoms, display dramatically increased levels of several xenobiotics in plasma. These results confirm that PK/PD parameters of commonly used drugs are highly modified in these patients. This suggests a potential role of xenobiotics in the pathophysiology of encephalopathy in patients with liver diseases.

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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 homeostasis through morphological plasticity. They adjust their volume by releasing osmolytes through neurotransmitter-receptors and ion-channels, modulate the neural circuits and control energy homeostasis through morphological plasticity. They adjust their volume by releasing osmolytes.

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). Decrease in the processes intersection was observed already at week4 post-BDL (Figure 1b). Although at week 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: ~18.7%; 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. 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.

REFERENCES

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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). In CHE impaired ammonium clearance by the diseased liver leads to brain glutamine accumulation. In-vitro, affected ammonium detoxification together
**A)** *Hippocampus - dentate gyrus*

**B)**

**C) Sholl analysis**

**D) Hippocampus - hilus**

**Cerebellum - granular layer**

**E)**

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: 500 μm.  
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: 25 μm.  
E) Sholl analysison 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* 'H-MRS – antioxidants detection as indirect OS sign

Hippocampus

- Glu
- Gln
- Pro
- t-Tyr

Cerebellum

- Glu
- Gln
- t-Tyr
- Pro

**Graphs**

- Gln
- Asc
- GSH

- Glu, Gln, t-Tyr, Pro

**Measurements**

- **Weeks after BDL**
- **Lactate**
- **Glu**
- **Gln**
- **t-Tyr**
- **Pro**

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

**Chemical Structures**

- COOH
- OH
- CO
- H2O2

**Images**

- ESR Silent
- ESR Active

**Graphs**

- Intracellular ROS generation rate

C) IHC staining with GPX1 - anti-oxidative enzyme

**Images**

- BDL
- SHAM

**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 $O_2^-$ 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 $O_2^-$. 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±2.2μm² (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 impair-
ment.5–8 ROS play an important role in cellular signaling, synaptic-plasticity, learning and memory. In
when in excess, they cause cellular damage.5–8 Systemic oxidative stress was previously shown in bile-
duct-ligated rats (BDL). Using in-vivo-longitudinal 1H-MRS we previously observed the indirect presence of OS as a decrease of brain Asc 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-MRS (Varian/Magnex/Scientific) using SPECIAL-sequence 7 (TE = 2.8 ms). Ex-vivo-ESR: ESR300E (Bruker-BioSpin) was used for intra-tumoral superoxide anion detection. Hippocampus cerebellum were extracted at weekends post-
BDL/sham-surgery (n = 9), incubated in medium with 10 mM-CHM-cell- permeable spin-trap (Nirynng GmbH). Immunohistochemistry (ICH): GPX1 (anti-oxidative-enzyme) staining was

RESULTS: In total, 94 cirrhotic patients who underwent LT at the Montreal University Hospital Center
were included. Sarcopenia was assessed at the third lumbar level vertebrae using a computed

REFERENCES
1. B. Base Metab Brain Dis 2013.

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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 SIPCHE score (formula of 4 SIP statements, gender and age). We here aim at externally validate SIPCHE score in a cirrhotic cohort using continuous
reaction time (CRT) test and postoperative hepatic encephalopathy score (PHES) for MHE diagnosis.

METHODS: 110 cirrhotic patients without OHE (age 60 years, MELD 11.4, 80% blue-collar)
corroborated 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 version) was applied and predictive values were calculated. We
followed the patients for 2.7 years on average and registered OHE episodes.

RESULTS: The SIPCHE was abnormal in 82/110 patients and was in agreement with the psychometric
tests in 73/110 cases (66%). The SIPCHE indicated MHE in 58/71 of the patients with MHE according to
two psychometry (positive predictive value = 71%, sensitivity = 82%, AUTROC 0.63). The SIPCHE
was false positive in 24/39-MHE patients (positive predictive value 38%, NPV 53%). A normal SIPCHE
did not exclude MHE in our population in 17/82 (46%) with a normal SIPCHE score had MHE according
to the CRT and PSE tests. In our cohort using a cut point of >2.00, in stead of >0.70, slightly
improved correct classification to 72% of patients. Only 42/24 (17%) with a normal baseline SIPCHE
experienced OHE, while 29/82 (35%) with abnormal SIPCHE experienced OHE (P = 0.05). Accord-
ingly, the SIPCHE 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 SIPCHE score is able to identify the majority of patients with MHE and future OHE episodes, but lacks diagnostic specificity. We speculatively
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.

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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 com-
plexations, including hepatic encephalopathy, in cirrhotic patients awaiting and after liver trans-
plantation (LT). 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 level vertebrae using a computed
tomography scan (CT-scan). The diagnosis 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 = 0.012), infections post-LT (P = 0.001) and readmissions (P = 0.0048) 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.
Hyponatremia Correction in Cirrhosis May Increase the Speed of Complex Information Processing

Hyponatremia is frequent in patients with advanced cirrhosis and ascites. A decrease in plasma osmolality exacerbates astrocyte swelling and through this mechanism may worsen cognitive function. Our objective was to determine whether, in patients with cirrhosis and ascites, an increase in plasma osmolality exacerbates astrocyte swelling and through this mechanism may worsen cognitive function. Improvement of hyponatremia was associated with an increase in the speed of complex information processing. Improvement of hyponatremia was achieved more frequently with satavaptan treatment, which showed a trend towards better results on cognitive function.

Acetate Attenuates the Astrocyte Swelling and Brain Edema in Severe Liver Failure

BACKGROUND: Astrocyte swelling and brain edema are major complications of severe liver failure. Ammonia plays a major role in the development of astrocyte swelling and brain edema in this condition. However, current therapies have not thus far improved the outcome of liver failure induced astrocyte swelling and 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 glyceryl triacetate (GTA), an acetate precursor, which is known to increase circulating acetate 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 mg/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.

Cholestasis Decreases Dendritic Spine Density in a Rat Hippocampal Organotypic Culture

BACKGROUND: Executive functioning impairment in children with cholestatic liver disease is increasingly recognized. Injury to developing neuronal networks could be an underlying mechanism.

METHODS: Ex vivo organotypic hippocampal slices were obtained from 6-old Wistar rats. They were maintained for 15 days in a CO2-incubator (33°C). pc-DNA3.1-EGFP plasmid biolistic transfection was performed 7 days after harvesting. 3 days following transfection, neurons exposed to MIX (0.154 vs 0.026 spines.)

RESULTS: At inclusion into the studies, patients with normonatremia exhibited better results on the TMT-A and TMT-B that could not be explained by differences on age. This group also exhibited better parameters of liver function (Table 1). Improvement of hyponatremia was associated with shortening on the time needed to complete TMT-B: $-20\text{ s vs }-6.5\text{ s (P = 0.02)}$, but not TMT-A: $-10\text{ s vs }-5\text{ s (P = 0.16)}$. Increase in serum osmolality was also associated with better TMT-B scores ($P < 0.001$ at Day 5-7 and $P = 0.033$ at Day 14-28), but this was not shown for TMT-A. Liver function parameters remained stable in both groups of patients. Improvement of hyponatremia at Day 5 was most commonly seen in patients that received satavaptan (59.7%, n = 82) than in those treated with placebo (18.5%, n = 28). Median changes in TMT scores with satavaptan (all doses pooled) compared to placebo were: TMT-A: $-10\text{ s vs }0\text{ (P = 0.08)}$ and TMT-B: $-20\text{ s vs }-7.5\text{ s (P = 0.12)}$.CONCLUSIONS: Improvement of hyponatremia in cirrhosis was associated with an increase in the speed of complex information processing. Improvement of hyponatremia was achieved more frequently with satavaptan treatment, which showed a trend towards better results on cognitive function.
Chronic hepatic encephalopathy (CHE) 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 matrixial 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 defective neuronal 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.

Support: VA Merit review; AASLD/ALF.

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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 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 mast cell activation diminished both AQP levels, as well as brain edema development. These findings strongly suggest that acute liver failure stimulates the activation of choroid plexus mast cells and the subsequent 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 choroid 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.

Support: VA Merit review; AASLD/ALF.

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Mechanism of Alzheimer Type II Astrocyte Development: Implication for the Defective Neuronal Integrity and Neurobehavioral Deficits Associated With Chronic Hepatic Encephalopathy

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ABSTRACT: 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 astrocytes is implicated in the pathogenesis of CHE. We therefore examined whether the brain-derived neurotrophic factor (BDNF) is involved in the development of Alzheimer type II astrocytes in the rat brain. Using a thioacetamide (TAA)-treated rat brain model of chronic liver failure, we 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 mast cell activation diminished both AQP levels, as well as brain edema development. These findings strongly suggest that acute liver failure stimulates the activation of choroid plexus mast cells and the subsequent 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 choroid 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.

Support: VA Merit review; AASLD/ALF.
CONCLUSIONS: Elevated cortical IGFBP3 expression contributes to the pathogenesis of HE in

**METHODS:**

- Elevated cortical IGFBP3 expression contributes to the pathogenesis of HE in patients with cirrhosis.
- A retrospective cohort study was conducted involving patients with cirrhosis and HE at the University College London Hospitals.
- Cortical IGFBP3 expression was evaluated using immunohistochemistry and western blots.

**RESULTS:**

- Elevated IGFBP3 expression was found in the frontal cortex of patients with HE.
- IGFBP3 expression was correlated with the severity of HE.

**CONCLUSIONS:**

- IGFBP3 may be a target for therapeutic intervention in HE.
- Further studies are needed to investigate the role of IGFBP3 in HE pathogenesis.

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**Phenotype Genomics in Hepatic Encephalopathy**

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Previously Identified Candidate Gene Associations in Hepatic Encephalopathy Do Not Replicate in the STOPAH Cohort

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**BACKGROUND:**

- Hepatic encephalopathy (HE) is a common complication of cirrhosis and negatively affects quality of life and prognosis.
- However, the development of HE is not inevitable, even in patients with severe hepatic decompensation.
- The STOPAH GWAS database was used to identify genetic variants associated with HE.

**METHODS:**

- Genotypic association analyses were undertaken for each of the genetic variants in nine candidate genes.
- Genotyping data from 731 participants in the STOPAH trial were analyzed.

**RESULTS:**

- No significant associations were found between the genetic variants and HE.
- The significance of the association was lost when the data were corrected for multiple testing.

**CONCLUSIONS:**

- The previously reported genetic associations with HE were not replicated in the present study.
- Further studies are needed to confirm the role of genetic variants in HE pathogenesis.

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**Genetically Engineered E. coli Nissle Attenuates Hyperammonemia and Improves Memory in an Experimental Model of Cirrhosis and Hepatic Encephalopathy**

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**BACKGROUND:**

- Hyperammonemia associated with chronic liver disease (CLD) is implicated in the pathogenesis of hepatic encephalopathy (HE).
- Gut bacteria, such as Escherichia coli, may contribute to the pathogenesis of HE.

**METHODS:**

- A genetically engineered E. coli Nissle strain was administered to mice with CLD and HE.
- The effects of the strain on ammonia levels, memory, and brain function were evaluated.

**RESULTS:**

- The engineered E. coli strain reduced ammonia levels and improved memory in mice with CLD and HE.
- The results support the potential use of probiotics in the treatment of HE.

**CONCLUSIONS:**

- Further studies are needed to evaluate the long-term effects of probiotics in HE treatment.
- Probiotics may be a promising therapeutic strategy for HE management.
While STM was resolved in BDL-SYNARG, patients with CLD and HE.

**RESULTS:**

BDL significantly increased ammonia over time, with levels of 109.1 ± 9.2 μM (Shams 56.7 ± 5.5 μM, P < 0.001) and 150.2 ± 25.6 μM (Shams 58.3 ± 10 μM, P < 0.001) at 3- and 5-weeks, respectively. In addition, plasma liver markers alanine-transaminase, aspartate-transaminase, bilirubin, and gamma-glutamyl transferase were significantly increased in BDL rats at both timepoints while albumin was significantly lowered. As compared to BDL-Veh rats, hyperammonemia was attenuated by SYNARG (103.9 ± 12.3 μM) and SYNARG+BUT (110.8 ± 8.5 μM) at 5, but not 3 weeks post-surgery, while liver fibrosis (hydroxyproline content) was attenuated at 5, but not 3 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 affected in all BDL groups without protective effects of treatments. Short-term memory (STM) was impaired in BDL-Veh (P < 0.001) and 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.

**REFERENCE:**


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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 5-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 at 5-weeks this was only found in Lean-BDL. These parameters were higher in Obese-BDL vs Lean-BDL vs 3- and 5-weeks. Plasma ammonia, bilirubin, albumin, ALT, AST, and ALP were impaired in Obese- and Lean-BDL vs respective Shams at 3- and 5-weeks. AST and ALP increased in Obese-BDL vs Lean-BDL at 5-weeks. Elevated HDL-cholesterol and decreased LDL-cholesterol were detected in Obese-BDL and Lean-BDL vs respective Shams at 3- and 5-weeks, while LDL-cholesterol was higher in Obese-BDL vs Lean-BDL at 5-weeks. Total-cholesterol increased in Obese-BDL vs all groups at 5-weeks. At 3 weeks, motor-coordination was reduced in Obese-BDL, but not in Lean-BDL vs respective Shams, while at 3-weeks, motor-coordination decreased in both Lean-BDL and Obese-BDL vs respective Shams with worse performance in Obese-BDL vs Lean-BDL at 3-weeks. Plasma ammonia, bilirubin, albumin, ALT, AST, and ALP were impaired in Obese- and Lean-BDL vs respective Shams at 3- and 5-weeks. AST and ALP increased in Obese-BDL vs Lean-BDL at 5-weeks. Elevated HDL-cholesterol and decreased LDL-cholesterol were detected in Obese-BDL and Lean-BDL vs respective Shams at 3- and 5-weeks, while LDL-cholesterol was higher in Obese-BDL vs Lean-BDL at 5-weeks. Total-cholesterol increased in Obese-BDL vs all groups at 5-weeks. At 3 weeks, motor-coordination was reduced in Obese-BDL, but not in Lean-BDL vs respective Shams, while at 3-weeks, motor-coordination decreased in both Lean-BDL and Obese-BDL vs respective Shams, with worse performance in Obese-BDL vs Lean-BDL at 3-weeks. At 3 weeks, skill-learning improved in all Shams and Lean-BDL, but not in Obese-BDL at 5-weeks contrary to Sham-groups, both BDL groups did not improve performance. Muscle-strength decreased in Lean-BDL and Obese-BDL vs respective Shams at 3- and 5-weeks. Hyperlocomotion and anxiogenic effects were detected in Obese-BDL, but not in Lean-BDL vs Shams at 5-weeks.

**CONCLUSIONS:** HFD induces obesity pre-BDL, which is maintained post-BDL, with a HCD-diet which was accompanied with increased fat-mass and hyperlipidemia. Neurological decline in obese-cirrhotic rats developed earlier and was more severe versus Lean-BDL rats. Besides, some neurological impairments developed in Obese-BDL but not in Lean-BDL. These results suggest a synergistic effect, which accelerates/worsens the disease-associated abnormalities in CLD and HE.