host-microbial interactions (FUT2), pro-inflammatory response triggered by pathogens (TLR-9) and glutamine transport (SLC1A3 and SLC1A5). Combining these genetic factors according to number of alleles at risk, three levels of risk patients were delineated: low, mid or high risk [sHR: 1; 6.5 (1.8–22.9) P < 0.001] (C-index = 0.82). This regression model performed in a similar manner in the validation cohort [sHR: 1; 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.

P: 2 Junior Investigator | Oral Presentation

Opioid Prescriptions Increase the Risk of Hepatic Encephalopathy in a National Cohort of Privately Insured Patients With Compensated Cirrhosis

Andrew M. Moon, MD, MPH; Yue Jiang, Shari S. Regal, MD, MPH; Elliot B. Tapper, MD; Sarah R. Lieber, MD1, A. Sidney Barritt IV, MD, MSCR1.

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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 (varical 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,
S2

2019 ISHEN Abstracts

P: 3 Junior Investigator | Oral Presentation

Clinical Value of Asterixis in a Large Population of Well-characterised Patients With Cirrhosis and Varying Degree of Hepatic Encephalopathy

Chiara Formentin, MD,[1] Chiara Mangoni, MD,[1] Matteo Tuoro, MD,[1] Michele De Rui, MD,[1] Lisa Zarantonello, PhD,[2] Paolo Angeli, MD,[1] Sara Montagnese, MD, PhD,[1]

1University of Padova, Padova, Italy.

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/graded 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 (ScanRT) reaction times). Laboratory indices (venous ammonia, CRP, sodium) were recorded, together with procedures and medications from 1 year before cirrhosis diagnosis to 3 months after cirrhosis diagnosis. Opioid exposure was assessed over a 6 month period after cirrhosis diagnosis. Exposure procedures and medications) from 1 year before cirrhosis diagnosis to 3 months after cirrhosis diagnosis to gabapentin and statins were assessed as positive and negative controls, respectively, to assure internal validity of the database. Our outcomes (HE and other decompensation events) were significantly associated with higher odds of developing HE. Positive and negative controls performed as expected, supporting the validity of the data. Given their potential risk, opioids should be minimized in patients with cirrhosis, even in the absence of prior decompensation events.

CONCLUSIONS: In this nationwide cohort of privately-insured patients with cirrhosis, opioid prescriptions were common and significantly associated with higher odds of developing HE. Positive and negative controls performed as expected, supporting the validity of the data. Given their potential risk, opioids should be minimized in patients with cirrhosis, even in the absence of prior decompensation events.

P: 4 Junior Investigator | Oral Presentation

Uncovering Sex-based Differences in a Rat Model of Chronic Liver Disease and Hepatic Encephalopathy


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 estrus 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 aim 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, we assessed estrus cycle phase (by cellular cytology), anxiety (open field test), motor incoordination (rotorod test) and night-time activity. We also assessed body weight, body composition (MRI), gastrocnemius muscle weight (circumference strength), and enzymes in plasma. Results from female BDL rats were compared to historical laboratory data from male BDL rats.

RESULTS: Female BDL rats had increased liver enzymes (ALP (P = 0.001) and AST (P = 0.0001) (but not ALT)), increased blood-brain barrier (BBB) permeability, neuropsychological and laboratory HE indices, as well as the likelihood of developing HE-related hospitalisations over time.

CONCLUSIONS: Asterixis is reliably detected/graded by specialist trainees in a tertiary referral liver centre, and shows significant associations with established neuropsychological, neurophysiological and laboratory HE indices, as well as the likelihood of developing HE-related hospitalisations over time.
P: 6  Junior Investigator | Oral Presentation

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

Jessie Xu1, Chathur Acharya1,2, Hugo Vargas3, Andres Duarte-Rajo3, James B. Wade2, Levy R. Thacker2, Megan Kelly4, Andrew Fagan3,4, Melanie B. White2,3, Christopher Flud1, Leroy R. Thacker2, Megan Kelly4, Andrew Fagan2,3, Melanie B. White2,3, Christopher Flud1, Leroy R. Thacker2, Megan Kelly4, Andrew Fagan2,3, Melanie B. White2,3, Christopher Flud1, Leroy R. Thacker2, Megan Kelly4, Andrew Fagan2,3, Melanie B. White2,3, Christopher Flud1

Mice injected with AOM had increased Let7f and decreased IGF1 expression in the RESULTS: qPCR and EIA. Microglia were stained by IBA1 and cortex neuroinflammation assessment at various time points. Neuroumucular deficits were assessed using a grip strength meter, and a dautymotor 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 immunoblotting, immunohistochemistry and/or qPCR. Microglia were stained by IBA1 and cortex field staining and cell morphology were assessed. In vivo, 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 cytokines, as well as the neuroinflammation were 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 antagomir 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). 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: 109 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 < 0.01; EncephalApp Off=On 181.4 ± 71.9 vs 218.2 ± 80.0, P = 0.03) and had a better QOL (SIP total 3.8 ± 7.1 vs 7.9 ± 9.5, Psych 3.1 ± 8.4 vs 7.2 ± 11.1, Phys 3.0 ± 6.2 vs 6.7 ± 9.5, all P < 0.01). 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% (n = 17) patients were positive for MHE on PHES compared to controls. On EncephalApp, 49% (n = 47) patients were positive. AUC for EncephalApp using PHES as the gold standard was 0.86 (0.78-0.95 CI).

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

P: 7  Junior Investigator | Oral Presentation

Identifying Overt Hepatic Encephalopathy Using Administrative Data in the ICD-10 Era: A Study to Validate Diagnostic Algorithms

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BACKGROUND: Administrative datasets are necessary in order to study the outcomes of patients with hepatic encephalopathy (HE) at the population-level. Validated algorithms using ICD-9
diagnostic codes have facilitated prior studies but are now invalied given the switch to ICD-10 in 2015. To date, no study has validated any diagnostic coding algorithm for HE using ICD-10 codes. 

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

RESULTS: Overall our cohort was aged 60 (52-66) years, 58.3% male, and 70% Child class A. All patients had portal hypertension, 76% had varices, and 41% had a history of ascites (predominantly well controlled). The median MELD-Na score was 9 (IQR, 7-13). Overall 68 out of 301 patients (22%) developed overt HE during follow up. Only 1 patient was assigned the code K72.91, whereas codes G93.40 and G93.49 were not coded in our claims data. Tables 3 codes, 4 coded, and sensitivity for HE based on ICD-10 codes were K72.90 (95%, high specificity (97.5%) and high specificity (97.9%), positive predictive value (PPV) 84.8%, and negative predictive value (NPV) 85.1%. Recorded lactulose and or rifaximin use was highly sensitive (94.1%) and specific (98.3%), PPV 87.7%, NPV 98.3%. CONCLUSION: In this prospective study, we define the performance of diagnostic codes for the identification of HE in the electronic health record study. Medications specific for HE therapy outperformed diagnostic codes.

P: 8 Junior Investigator | Oral Presentation

Assessment of Cirrhotic Patients With Covert Hepatic Encephalopathy (HE) Through the EncephApp (Stroop-Test) Based on Critical Flicker Frequency and PHES-Test R.M. Neyl,1 G. Kircheis1, N. Hilger1, S. Lüth1. 1Department of Gastroenterology, Hepatology and Diabetology, Center of Internal Medicine II, Brandenburg Medical School, University Hospital Brandenburg, Cottbus, Germany.

BACKGROUND: In daily clinical practice, the detection of HE is still less represented but strongly improved. 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 On-Plus-Off Time of the EncephApp was compared to the results of the CFF and the PHES-Test. Different Cut-Offs of the On-Plus-Off Time were analyzed. Within these HE groups, the mean values of the PHES-Test, the CFF and the On-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 sensitivity and specificity were calculated. The comparative parameter was the result of the PHES-Test. Through the creation of a ROC curve, the AUC (area under the curve) showed that the Cut-Off time of >224 sec with a sensitivity of 93% and a specificity of 98% (82%). Other Cut-Off values showed lower sensitivities and higher false negative values.

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

P: 9 Junior Investigator | Oral Presentation

Pharmacotherapies that Specifically Target Ammonia for the Prevention and Treatment of Hepatic Encephalopathy in Adults With Cirrhosis Harry D. Zacharias,1,2 Meeke Dirks,1,3 Carlotta Petrusha,1 Annemarie Goldbeker,1,2 Anika Blanka Tryc,1,3 Hannele Honvold Berg-Hodb,1,3 Christian Strausburg,1,3 Jurgen Klempnauer,1,3 Karin Weissenborn,1,3 Henning Pfliugfeld,1,3 1Hannover Medical School, Hannover, Germany.

BACKGROUND: Cognitive dysfunction caused by hepatic encephalopathy in patients with acute or chronic liver failure improves within the first year after liver transplantation. However, cognitive restitution seems to be incomplete in a subset of patients. Furthermore, a new-onset cognitive decline after liver transplantation was described. This prospective study analyzed whether a history of hepatic encephalopathy before liver transplantation had an impact on the long-term outcome of cognitive function after liver transplantation and if patients who underwent liver transplantation up to 5 years before showed worse cognitive function than adjusted healthy controls.

METHODS: 34 patients with liver cirrhosis on the waiting list for liver transplantation underwent a psychometric battery and questionnaires assessing health-related quality of life 3.4 ± 2.1 months (T1) before liver transplantation. Further 33 patients were included directly after liver transplantation. After transplantation all patients (n = 67) underwent psychometric testing and completed questionnaires at 3.4 ± 2.1 months (T2) before transplantation and at 3.4 ± 2.1 months after transplantation (T3). The psychometric test battery consisted of the Postoperative Encephalopathy Syndrome Test which provides the psychometric hepatic encephalopathy score (PHES), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Inhibitory Control Test and the Critical Flicker Frequency. All patients were asked to complete the self-reporting questionnaires Hospital Anxiety and Depression Scale, Beck Depression Inventory, Fatigue Impact Scale and Short Form 36 health survey to assess health-related quality of life.

CONCLUSIONS: Patients tested before liver transplantation performed significantly worse than controls in the psychometric tests (RBANS total mean scale 96.2 ± 13.3 vs 99.9 ± 12.0, P = 0.011; PHES mean scale 0 (IQR – 2, 1) vs 1 (IQR 0, 2), P < 0.01). About 1 year after liver transplantation patients with a history of hepatic encephalopathy still showed cognitive impairment compared to controls (liver transplantation vs. controls, difference in mean scale difference 2.2± 1.2, P = 0.001). Cognitive impairments associated to hepatic encephalopathy seems to be reversible within 5 years after liver transplantation.

P: 11 Junior Investigator | Oral Presentation

Cognitive Improvement After Capsular Fecal Microbiota Transplant in Hepatic Encephalopathy Is Associated With Changes in Microbial Function and Inflammation Dr. Chatur Acharya1, Nita Salzman2, Dr. Genta3, Masoumeh Sikaroodi1, Michael Haywood2, Andrew Fagan3, Edith A. Gavis3, Ms. Melanie White4, Mr. Hajime Takei6, Dr. Hiroshi Nittono6, Dr. William M. Pandak Jr1, Dr. Phillip B. Hylemon4, Patrick M. Gillevet5, Jasmohan S. Bajaj1.

BACKGROUND: Microbiota can transform BAs by deconjugating, converting primary to secondary BAs & tertiary(oxo, phenolic) BAs. This interaction is responsible for the pathogenesis of inflammation, bacterial translocation, microbial function, bile acid, BA with cognition needs to be evaluation. Gut microbiota can transform BAs by deconjugating, converting primary to secondary BA (Acetone, sultone, ursodeoxycholic acid), formation. Aim: Determine changes in fecal microbiota vs. placebo + rifaximin, with cognition as the primary outcome. METHODS: 20 cirrhotics with recurrent HE on lactulose/rifaximin were randomized 1:1 into 15 FMT capsules once vs identical placebo. FMT was from a single donor enriched in Lachnospiraceae/Ruminococcaceae, which are associated with secondary BA generation. We collected stool/blood &...
Figure 1: Effect of treatments which specifically target ammonia on hepatic encephalopathy in cirrhosis

### RESULTS:

**Bacteria:** There was a significant increase in secondary/primary BA ratio (Figure 1c) in FMT pts. Deconjugation and tertiarBAs remained similar between groups. Correlation network complexity was compared between post-FMT vs post-placebo states.

**Correlation networks between BAs, microbiota, LBP, IL-6 and cognition were created. Correlation network complexity was compared between post-FMT vs post-placebo states.**

**Blood Culture:** A reduction in LBP & IL-6 was seen only in FMT pts and negatively with inflammation.(IL6 redlines) and associated with better cognition (EncephalApp; high score post-FMT (Figure 1f) compared to placebo at study end.

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[10]
The Role of Monocarboxylate Transporter-1 and Lactate Metabolism on the Development of Cognitive Deficits During NAFLD

Anna Hadjihambi, PhD1, Patrick S Hosford, PhD2, Rajiv Jalan, PhD, MD,3,4,5, Luc Pellerin, PhD1.
1UNIL, Department of Physiology, Lausanne, Switzerland; 2Centre for Cardiovascular and Metabolic Neuroscience, Neuroscience, Physiology and Pharmacology, University College London, London, UK; 3UCL Institute for Liver and Digestive Health, London, UK; 4Division of Medicine, University College London Medical School, London, UK; 5Royal Free Hospital, London, UK.

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 1 high fructose/high glucose in water [HF/HG]) we investigated the development of cognitive deficits and state of cerebral oxygenation and cerebrovascular reactivity.

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

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

CONCLUSIONS: Our results suggest that NAFLD is associated with a depression-related behaviour and a trend of decreased cerebral PO2 baseline. MCT1 haploinsufficient mice were resistant to the reported phenotypes, suggesting a link between liver metabolism and neuropathophysiological alterations in NAFLD.
Non-alcoholic Fatty Liver Disease Alters Expression of Genes Governing Hepatic Nitrogen Conversion

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

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

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

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

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

CONCLUSIONS: NAFLD downregulated the expression of urea cycle-related genes. 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 PHES score, CogstateTM computerised psychometric testing, W'TAR and SF6 scores. Color-naming subset of the Stroop task was significantly impaired at baseline in LOLA receivers ($P = 0.0179$) For group averaged whole-brain data, there was no significant difference in activation for both motor and cognitive tasks or in resting state in all 34 patients at baseline and 12 weeks. Group differences by region of interest (see Table 1 below) the choice reaction time task in the default mode network (DMN) demonstrated significant treatment ($P = 0.0262$) advantage after 12 weeks of LOLA. Of the 12 resting state networks studied, visual area 2 showed a significant treatment ($P = 0.0211$) benefit after 12 weeks of LOLA.

Conclusion: In the first RCT of LOLA combined with modern brain imaging analysis, a significant treatment benefit with LOLA on task activation was noted in the DMN. A significant treatment advantage of LOLA on resting-state fMRI in the visual network is consistent with this, this may be a compensatory mechanism in early MHE. Future studies could stratify patients who may benefit from LOLA based on 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
Patricia Pringle Bloom, MD1,2
1Massachusetts General Hospital, Boston, MA, USA.
2Boston, MA, USA.

BACKGROUND: Model for end-stage liver disease-sodium (MELD-Na) score and extrahepatic organ failures (EHOFs) predict poor outcomes in cirrhotic patients, including those with hepatic encephalopathy (HE); however, there is a need for the development of additional and specific predictors for outcomes in HE. We aimed to determine if cognitive testing, total daily lactulose dose (TLD), 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. Test-and-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 ($P = 0.71$) or MOCA score ($P = 0.51$).

CONCLUSIONS: Traditional prognostic tools in cirrhosis, including MELD-Na and EHOFS, were superior to cognitive assessments, total daily lactulose dose, and stool frequency in predicting 30-day outcomes for those admitted with overt HE. Future studies should evaluate MELD-Na and the presence of EHOFS as determinants of discharge readiness or discharge destination in patients admitted with cirrhosis and HE.
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[15]
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 14 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 value <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 Hadjihambis, PhD1,2, Patrick S. Hofroid, PhD3, Abeba Haltețion2, Nathan Davies, PhD2, Alexander V. Gourine, PhD3, Rajiv Jalan, PhD, MD2.

1Universite de Lausanne, Department of Physiology, Lausanne, Switzerland; 2UCL Institute for Liver and Digestive Health, Division of Medicine, University College London London Medical School, Royal Free Hospital, London, UK; 3Centre for Cardiovascular and Metabolic Neurosciences, 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 hypoperfusion in patients with HE indicated that cerebral oxygen supply could also be compromised (Dam et al., 2013). Decreased lactate and reduced oxygen supply may lead to CNS energy deficiency and have important neurological consequences, particularly in patients with advanced cirrhosis. In this study we assessed cerebral tissue oxygen tension and CO2 cerebrovascular reactivity in an animal model of HE.

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

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

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

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

Rahmatullah Bhatti1,2

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 patients of encephalopathy and effect of animal proteins consumption during the festival of EID-UL-ZAH

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-ZAH and Group B includes patients admitted on EID UL ZHAH 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 54.36 ± 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 factors) 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-ZAH, majority had consumed high (animal) proteins. Consumption of meat (animal proteins) could be the possible contributing factor. Generally protein restriction is not recommended in cirrhosis 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.

REFERENCES

P: 21 Junior Investigator

Changes in Cerebral Hemodynamic Parameters in Patients With Acute Liver Failure

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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.2,3 Transcranial Doppler ultrasound (TCD) is a non-invasive device that can continuously measure the speed of cerebral blood flow, producing a velocity-time waveform that indirectly monitors changes in cerebral hemodynamics, making it very useful in patients with ALF.4,5 Objectives Compare the cerebral hemodynamic parameters in patients with ALF using TCD before and after liver transplantation.

METHODS: Retrospective and descriptive study. We searched patients with ALF during the period 2014–2018, who underwent TDC. For the descriptive analysis, medians of the quantitative variables and percentages of the qualitative variables were used. The comparison of medians was made using t student. Values were expressed as median and interquartile range, analyzed with Mann-Whitney U test. A value of P < 0.05 was considered statistically significant.

RESULTS: We studied 10 patients (9 women, 1 man), with a median age of 29 years. The etiology of the liver failure was the following: 50% for autoimmune hepatitis, 20% undetermined, 10% hepatitis A and 10% pharmacological. We identified 4 deaths, 1 of which was during the post-transplant period. The following parameters were measured: systolic peak velocity (SPV), final diastolic velocity (F DV), medium velocity of the middle brain artery (VMD), resistance index (RI) and pulsatility index (PI). There were changes in RI and PI, before transplant TDC: RI 0.69 (0.56–0.71) PI 1.29 (0.96–1.37) and after transplant TDC RI 0.51 (0.40–0.58), PI 0.78 (0.55–0.95) P value = 0.005 and 0.005 respectively.

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

REFERENCES

P: 22 Junior Investigator

Deficit of Short Working Memory in Rat With Thioacetamide-Induced Progressive Acute Hepatic Encephalopathy Involving Serotonin Innervation and Astroglia Dysfunctions

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

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

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

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

P: 23 Junior Investigator

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

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1Asian Institute of Medical Sciences (AIMS), Hyderabad, Pakistan.
CONCLUSIONS: Acute-on-chronic liver failure (ACLF) is an acute deterioration of liver function found to be predictors of mortality of ACLF.

METHODS: We conducted a prospective descriptive study at AIM (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 induced liver injury (DILI) 8 (6.8%), HEV acute hepatitis 7 (5.9), HDV superinfection 5 (4.3%), HBV flair 4 (3.4%), alcohol binge drinking 4 (3.4%), surgery 2 (1.7%), acute PVT 2 (1.7%), Upper GI Bleed 1 (0.9%) and 20 (17.1%) were unknown. Hospital mortality was 49 (41.9%), 28 days 71 (60.7%) and 12 weeks mortality was 103 (88.0%). Organ failure (P < 0.002), ACLF grade (P < 0.001), encephalopathy (P = 0.001), MELD (P = 0.01) and AKI (P = 0.02) were found to be predictors of mortality.

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

**P: 24 Junior Investigator**

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

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

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

Astroglia was assessed through an immunohistochemical analysis using anti-GFAP antibody on frontal sections of the hippocampus following.

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

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

**P: 25 Junior Investigator**

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

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

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

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

CONCLUSIONS: Myosteatosis and sarcopenia, probably by reducing the handling of ammonia in the muscle, are independently associated to MHE and to the risk of overt HE in cirrhosis. In malnourished patients, the amelioration of nutritional status may be a possible goal to decrease both the prevalence oh MHE and the incidence of overt HE.
The Modification of Quantity and Quality of Muscle Mass Improves the Cognitive Impairment After TIPS
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1Sapienza Università di Roma, Rome, Italy.

BACKGROUND: Hepatic encephalopathy (HE) is the major complication of transjugular 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.

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 = 0.0005; plasma ammonia: 48.5 ± 28.7 vs 96 ± 31.5 µg/dl; P = 0.0004) was significantly reduced in the patients with improved SMI. MELD remained stable or worsened after TIPS and was not significantly different between the groups with or without SMI improvement.

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

Evaluation of Neurocognitive Function in Patients With Compensated and Decompensated Cirrhosis
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2Universidad Autónoma Metropolitana, The American Journal of GASTROENTEROLOGY

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 apexa 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 ± 1.82. MELD Na mean for total patients was 12.98 ± 5.04. Of the masters, Reading Writing with 4.50 ± 0.89 for compensated and 4.85 ± 0.50 in decompensated (P = 0.07), in the domain of Executive Motor Functions with 5.69 ± 1.8 for compensated and 6.24 ± 0.89 decompensated (P = 0.16).

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

Decreased Mean Kurtosis in the Putamen Is a Diagnostic Feature of Minimal Hepatic Encephalopathy in Patients With Cirrhosis
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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. T2-weighted 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 = 0.16). Moreover, the prevalence of minimal HE (12.5% vs 73%, P = 0.0005; plasma ammonia: 48.5 ± 28.7 vs 96 ± 31.5 µg/dl; P = 0.0004) was significantly reduced in the patients with amelioration in 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.

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

<table>
<thead>
<tr>
<th></th>
<th>SMI improvement&lt;10% (n=11)</th>
<th>SMI improvement&gt;10% (n=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal HE (PHES&lt;4)</td>
<td>8/3 (72.7%) / (27.3%)</td>
<td>2/14 (12.5%) / (87.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>PHE5 score</td>
<td>-4.8±2.1</td>
<td>-1.6 ±2</td>
<td>0.0005</td>
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<tr>
<td>Overt HE (yes/no)</td>
<td>9/2</td>
<td>10/6</td>
<td>0.3</td>
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<tr>
<td>OHE in the first 3 months (N of episodes/pt)</td>
<td>0.9±1.04</td>
<td>0.6±0.5</td>
<td>0.3</td>
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<tr>
<td>OHE in the following months (N of episodes/pt)</td>
<td>1.4 ±1.4</td>
<td>0.06 ± 0.3</td>
<td>0.001</td>
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<tr>
<td>Venous plasma Ammonia (µg/dl)</td>
<td>96 ± 31.5</td>
<td>48.3 ± 28.7</td>
<td>0.0004</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>11.9 ± 6.2</td>
<td>11.4 ± 6.7</td>
<td>0.8</td>
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</table>
CONCLUSIONS: DKI detects changes in the cerebral white matter and basal ganglia regions of the subjects with liver cirrhosis. 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, 0.80, 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.

P: 29 Junior Investigator

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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<td>MK_WM</td>
<td>0.84</td>
<td>0.93</td>
<td>0.89</td>
<td>0.79</td>
<td>0.73</td>
<td>0.92</td>
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<tr>
<td>MK_CN</td>
<td>0.76</td>
<td>0.58</td>
<td>0.78</td>
<td>0.71</td>
<td>0.64</td>
<td>0.83</td>
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<tr>
<td>MK_Put</td>
<td>0.90</td>
<td>0.74</td>
<td>0.89</td>
<td>0.86</td>
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<tr>
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<td>FA_GP</td>
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</table>

0.29, respectively) when compared with the non-MHE group (0.16, 0.21, and 0.32, respectively) (P = 0.012, 0.002, and 0.0001, 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, 0.80, 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.

P: 30 Junior Investigator

Relation Between Mortality and Psychometric Test Results in Patients Awaiting Liver Transplantation


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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 Portosystemic 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 Portosystemic 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 < 0.0001). 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 = 0.193; 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.

P: 31 Junior Investigator

The Natural History of Cirrhosis After the Development of Hepatic Encephalopathy
Jeremy Louisaint, MD, Elliot B. Tapper, MD.
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 1.14, CI 1.12, P < 0.001). Factors that were inversely associated with hospital utilization were Rifaximin use (HR 0.40, CI: 0.39–0.42) and gastroenterology consultation (HR 0.73, CI: 0.67–0.80). Rifaximin use was associated with decreased hospital-days (HR 0.83, CI: 0.73–0.93) 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.

P: 32 Junior Investigator

Liver Transplant Is Associated With Improvement in Cognition, Tandem Gait and Risk of Falls
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P: 33  Junior Investigator

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

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BACKGROUND: Chronic hepatic encephalopathy (CHE) is a severe complication of chronic liver disease (CLD) characterized by cognitive and motor deficits. The diseased liver fails to metabolize toxins from the blood (ammonium, bilirubin etc.) which accumulate in the blood and brain. 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 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 analysed 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 + abnormal TD, 38 (62%) had prior OHE & 9 (14.7%) had falls. The abnormal vs normal TD pts had similar ages, sex, education level and MELD scores. Comparison showed the abnormal TD group had higher OHE (76% vs 48%, P = 0.03) and worse physical SIP score [24 (12.5, 39) vs 13.8 (3.2, 20.5), P = 0.008]. On multivariable analysis with abnormal TD as dependent variable physical SIP score was significant [OR 1.05 (1.006–1.09), P = 0.02]. On multivariable analysis with CHE + abnormal TD as dependent variable physical SIP score [OR 1.12 (1.06–1.25), P = 0.02] and PHES scores were significant [OR 0.8 (0.68–0.96), P = 0.02]. Post-LT 6/12 months: Six pts had ACR that was managed with standard treatment and all pts were controlled on calcineurin inhibitors and mycophenolate at post-LT visits. There was a sustained improvement in PHES, SIP scores, falls and TD abnormalities post-LT more at 12 compared to 6 months in all pts (Table 1). Post-LT analysis showed that pts with abnormal pre-LT TD had a worse PHES score at 6 months (~4 (~5, 0) vs ~0.5 (~3, 1.25), P = 0.0064) and higher cognitive impairment on PHES [12 (40%) vs 3 (10%), P = 0.007] compared to those with normal pre-LT TD.

CONCLUSIONS: After LT, there is a sustained improvement in CF, abnormal TG and HRQOL from 6 through 12 months, which is accompanied by a lower rate of falls.

 METHODS: Hippocampus (n = 7), cerebellum (n = 8) and striatum (n = 4) of adult male Wistar rats were scanned longitudinally using in-vivo 1H-MRS (SPECIAL sequence-TE = 2.8 ms, quantification with LCM) 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 osmoties (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 osmoties than hippocampus (Figure 1d). Also, trend towards a decrease in NAA and PE was observed uniquely for striatum (data not shown). A tendency of increase in Lactate was observed being the strongest for cerebellum (+84%-cerebellum, +8%-hippocampus, +5%-striatum) indicating a possible energy metabolism perturbation (Figure 1f). Brain regions displayed different antioxidant response with a decrease in Ascorbate being strongest in cerebellum (data not shown).

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

REFERENCES

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2019 ISHEN Abstracts 517

WITHDRAWN

P: 35  Junior Investigator

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

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

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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 = 85). OFs (Liver, Renal, Brain, Coagulation, Respiratory, and Circulatory) and ACLF grades were measured on Day 0, with CLIF 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). Overall, HE was higher in non-survivors (n = 191) compared to survivors (n = 116).

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.

P: 36
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
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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.1 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 of 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).2

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 x 2.8 x 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). 1H-MRS revealed some significant differences between the ‘high-dose rifaximin’ group at week 6 and at week 8, both in absolute value and relative to week 2 (+42% vs +118% at week 8, Figure 1b). Moreover, a decrease of glutamine was observed between week 4 and week 6 in the ‘high-dose rifaximin’ group (~10%), contrary to the non-treated group (Figure 1b). Also, in the ‘high-dose rifaximin’ group, decreases in the following metabolites were less pronounced during the time course of the study: myo-inositol, taurine, glutamate, ascorbate, 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.5,6

REFERENCES
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).1,2

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 (FIBROMIXX, 60 billion bacteria/kg of rat) started two weeks before BDL-surgery until the end of the study. Rifaximin (15.7 mg/kg/day – human-dose) 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 rise of brain glutamine (+33% 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 −13%, respectively). Also, bifidobacteria concentration was slightly higher in the ‘probiotics + rifaximin’ group at week 8 (Figure 1b). Finally, the administration of rifaximin associated with this probiotic showed more beneficial effects than rifaximin only, and both could be used to maintain a balanced microbiota and may provide opportunities for reducing the spread of antibiotic resistances.

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

REFERENCES

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 >65), 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] in rifaximin-treated and 16 [14–18] vs 16 [14–18] in 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-naïve 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 0.76], 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 [-12.25 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 [-3.45 to 1.13], 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>
</tr>
</tbody>
</table>

**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 + HA, n = 10), TLR4-/- control (TLR4-/-, n = 10) and TLR4-/- with HA (TLR4-/- + HA, 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^-ΔΔCT compared to sham/WT) of the 5 urea cycle enzymes (UCEs) were assessed. For study 2, protein expression of the key, rate-limiting enzyme carbamoyl phosphate synthetase 1 (CPS1) was also assessed (Western Blot, immunohistochemistry).

**RESULTS:** Study 1: There was a stepwise increase in plasma ammonia throughout sham, BDL and BDL+LPS groups (P < 0.001). Pre-treatment with TAK242 prior to LPS injection in BDL rats was effective in reducing plasma ammonia levels compared to BDL and BDL+LPS groups. Study 2: TLR4-/- mice were protected from HA compared to WT mice treated with HA. TLR4-/- mice treated with HA had lower plasma ammonia levels compared to WT mice treated with HA.

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

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

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

P: 40  Junior Investigator

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

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

RESULTS: The diet induced hypokalemia of 1.9 ± 0.4 mmol/L compared to pair-fed controls (3.6 ± 0.2 mmol/L). Muscle and kidney tissue potassium concentrations were decreased, whereas protein expressions of albumin, the urea cycle enzymes, and glutamine synthetase 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.

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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 aims to evaluate the change in common precipitants of HE, in-hospital mortality and its predictors.

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

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

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

P: 42  Junior Investigator

To Assess Frequency of Hepatic Encephalopathy in Spontaneous Bacterial Peritonitis Patients  

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

METHODS: This cross-sectional study was conducted at the Gastro-hepato-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 serology was HCV (61.7%). 21 were CTP B (17.5%) and should be restrained.

RESULTS: 108 patients were Child C (82.5%). HE was present in 75 (62.5%) with most common grades were II (29.33%) and II (26.7%) females were examined. Most common serology was HCV (61.7%). 21 were CTP B (17.5%) and should be restrained.

P: 43  Junior Investigator

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 is independent or insensitive. Our AIM was to evaluate a novel protocol for measuring brain water content in rats.

METHODS: 41 g bw) undergoing a 3-hour protocol for stress. Iba-1 has been found to be a highly specific and sensitive marker of microglial activation, which mediates the inflammatory response in the brain.

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 serology was HCV (61.7%). 21 were CTP B (17.5%) and should be restrained.

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Figure 1

A

![Graph showing brain swelling and liver function tests](image)

-Brain swelling (% water)
-ALT (U/L)
-Creatinine (µmol/L)

B

![Graph showing caspase 11 activity](image)

- Caspase 11 activity (arbitrary units)

-CCl4
-CCl4 + LPB

C

![Graph showing brain swelling and liver function tests](image)

-Brain swelling (% water)
-ALT (U/L)
-Creatinine (µmol/L)

- WT
-Casp11-/-
a prognostic biomarker in patients with cirrhosis remains unclear as there is no direct correlation with hyperammonemia and the manifestation of HE per se. It has recently been demonstrated that blood ammonia levels correlate with organ failure and are an independent risk factor for mortality in patients with cirrhosis and acute decompensation. The aim of this study was to determine whether ammonia levels in patients with advanced cirrhosis awaiting liver transplantation influence waiting list outcomes.

**METHODS:** A retrospective observational study of 300 sequential cirrhotic adult patients listed for liver transplantation between January 2015 and December 2018 was undertaken. All patients had an arterial ammonia measured at the time of assessment for transplant. All patients were closely followed up until death or transplantation. The main outcomes were hospital admissions (and number of organ failures), infection, mortality 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 (1.6%) 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. In multivariate analysis, ammonia correlated with hospitalisation ($P < 0.001$), 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 ($P < 0.001$).

**CONCLUSIONS:** In this retrospective study, arterial ammonia at the time of assessing 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.

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

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

**RESULTS:** A total of 115 patients were recruited. Forty-four patients (12.4%) died during the study period due to complications of liver cirrhosis other than HE. Of 67 subjects follow-up data were available in accordance with the protocol. After a median of 113 days half of the per protocol cohort (N = 34) was re-admitted due to a recurrent manifestation of HE. The patients 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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P: 47  
**Junior Investigator**

**Risk of Recurrent Hepatic Encephalopathy (HE) in Patients With Liver Cirrhosis: A German Registry Study**

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P: 48  
**Junior Investigator**

**Nonselective Beta-blocker Use Is Associated With Increased Hepatic Encephalopathy-Related Readmissions in Patients With Cirrhosis**

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**BACKGROUND:** Hepatic Encephalopathy (HE) is a reversible syndrome of impaired brain function that is associated with frequent hospitalizations and decreased survival in cirrhotic patients. Nonselective beta-blockers (BBs) are widely used as a first-line therapy for the prevention of HE and their association with increased hospitalizations in patients with cirrhosis is still unclear.

**Objectives:** This study aimed to assess the impact of nonselective BBs on HE-related hospitalizations in patients with cirrhosis.

**Methods:** A retrospective, single-center study was conducted on patients with cirrhosis who were admitted to the hospital for HE between 2001 and 2019. Patients were divided into two groups: those who received nonselective BBs and those who did not. The primary outcome was the number of HE-related hospitalizations. Additional outcomes included the number of all-cause hospitalizations, the number of HE-related rehospitalizations, and the mean length of hospital stay. Multivariate logistic regression analysis was performed to identify factors associated with increased hospitalizations.

**Results:** A total of 192 patients were included in the study. The nonselective BB group consisted of 96 patients, and the non-HE group consisted of 96 patients. The nonselective BB group had a significantly higher number of HE-related hospitalizations (P = 0.03) and a higher number of all-cause hospitalizations (P = 0.02). The mean length of hospital stay was also significantly longer in the nonselective BB group (P = 0.01). Multivariate analysis revealed that nonselective BB use was an independent risk factor for increased hospitalizations (P = 0.04).

**Conclusions:** Nonselective beta-blocker use is associated with increased HE-related hospitalizations in patients with cirrhosis. These findings highlight the need for further research to identify effective strategies to reduce hospitalizations in this vulnerable population.
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 hazard regression model. The model was adjusted for age, sex, Model for End-Stage Liver Disease (MELD) score, selective beta-blocker (SBB) use, ascites, and history of esophageal varices (EV) and transjugular intrahepatic portosystemic shunt (TIPS). The Kaplan-Meier method and log-rank test were used to compare the cumulative incidence of HE-related readmissions between the aforementioned groups.

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

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

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

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

METHODS: We recruited cirrhotic outpatients and controls between ages 25–70 years, were current drivers, were candidates for MBI & free of alcohol/drug use. 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 15 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 for the driving task complexity increased from No-traffic to Traffic to Traffic+Distractor states, we observed a shift of increased activation from parietal (precuneus, supramarginal and angular gyrus) and visual (lingual gyrus, V1 and V2) to frontal (dorsolateral prefrontal cortex, anterior cingulate cortex), and sub-lobar regions (caudate, putamen, pallidum, insula, and thalamus). This pattern reveals a gradual shift from basic visuo-spatial to complex performance brain regions regardless of control or cirrhosis group. Between-group activations: During both Traffic and Traffic+Distractor conditions, cirrhotic patients showed significantly lower activation than controls in brain regions associated with top-down attentional processing (posterior cingulate cortex), error detection and conflict monitoring (anterior cingulate cortex), attentional resource allocation (paracingulate gyrus), visual attention regulation (superior parietal lobule), inhibitory control (left middle frontal gyrus) and regions associated with regulation of voluntary movement (left pallidum, putamen) (Figure 1c).

CONCLUSIONS: Using MRI-compatible driving simulation, patients with cirrhosis demonstrated suppressed attention regulation circuits and sensorimotor control compared to controls, which worsened when distractors such as cellphone use were included. This is likely the neural basis for impaired driving skills in cirrhosis.
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-encephalopathy 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 as vehicle for non-episodic groups. Two days following the last HE episode, we assessed motor coordination (Rotarod), 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 (≥ 30.4%), P = 0.06) in episodic compared to non-episodic BDL rats, suggesting that although episodic-BDL rats recover from each HE episode, baseline (pre-episode) ammonia remain higher than non-episodic BDL rats.

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

P: 51
Junior Investigator

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 agents, together with di fucosyl N-acetylneuraminic acid (NAD) and other active treatment, for the management of HE in adults with cirrhosis. The present study was performed to evaluate the efficacy and tolerability of aminoglycosides (NADs) and metronidazole in the prevention/treatment of episodic HE.

METHODS: A total of 1110 participants reported data on HE. No differences were found in any of the trials (RR 1.10, 95% CI 0.89 to 1.42, I2 6%). Mortality was low or very low for all outcomes. Twenty trials, with 1110 participants, reported mortality data, with 100 being suitable for analysis. Mean age of the patients was 59 (IQR 18, 79) years. 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 in relation to their neuropsychiatric status that either of the spectral variable. Thus, significant differences were observed in the visual background activity between all patient groups and controls and between patients with minimal and overt HE, whereas significant differences in spectral variables were only observed in the patients with overt HE (Figure 1).

CONCLUSIONS: The present study confirms that ‘visual assessment of the EEG, does not allow reliable grading’ and that ‘quantitative assessment may improve the reliability of EEG assessment is not supported by the findings in this study.

P: 53
Junior Investigator

Extent of Sarcopenia Does Not Correlate With Degree of Minimal Hepatic Encephalopathy in Patients on Treatment for Hepatic Encephalopathy
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BACKGROUND: Minimal hepatic encephalopathy affects over half of the patients with cirrhosis. It leads to deterioration of quality of life due to cognitive deficit. Both presence of sarcopenia and postsystemic shunts have been implicated in development of minimal hepatic encephalopathy. We retrospectively assessed the significance of sarcopenia and presence of postsystemic shunts in patients with minimal hepatic encephalopathy. METHODS: Patients with cirrhosis of liver attending the liver clinic at University of Padua underwent a detailed elective outpatient assessment for neurocognitive function. This included Psychometric Hepatic Encephalopathy Score (PHES), computer based tests, and EEG. We then selected patients who underwent a computed tomography for any reasons within 3 months of the neurocognitive assessment. The degree of sarcopenia and presence of postsystemic 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 in relation to their neuropsychiatric status that either of the spectral variable. Thus, significant differences were observed in the visual background activity between all patient groups and controls and between patients with minimal and overt HE, whereas significant differences in spectral variables were only observed in the patients with overt HE (Figure 1).

CONCLUSIONS: The present study confirms that ‘visual assessment of the EEG, does not allow reliable grading’ and that ‘quantitative assessment may improve the reliability of EEG assessment is not supported by the findings in this study.

P: 54
Junior Investigator

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

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

RESULTS: We enrolled a total of 257 patients with mean age 61.1 ± 8.3, 72% were males, HCV was the predominant etiology 96 (37.3%). Median BMI was 29 (26, 34). Median education was 13 (12, 16) years. Median MELD was 11 (7.25, 15) with median Childs 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 (7, 0) whereas 206 (80%) tested positive on encephalopathy stroop. On univariable analysis hypertension was found to be significant only for stroop. On multivariable analysis age and prior OHE were predictive for both tests but for the Encephalopathy stroop hypertension was found to be independently predictive (Table 1).

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

P: 55

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

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CONCLUSIONS: Decreased cognitive performance is associated with reduced rs-FC and GM atrophy in MHE patients. These changes could have a 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).

P: 56

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 functions 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 clinical practice.
Thrombospondin-1 Worsens Azoxymethane-Induced Hepatic Encephalopathy Through Activation of Transforming Growth Factor Beta 1

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 reaction latency and ataxia measurement. Liver histology was assessed by hematoxylin and eosin staining and serum transaminases were measured. Cleaved caspase 3 immunohistochemistry and TUNEL staining were used to assess apoptosis in liver tissue. Hepatic inflammation was determined by measuring IL-1β, IL-6 and TNFα expression via real-time PCR and ELISA assays. TGFβ1 and TSP-1 expression were assessed in liver, serum and cortex by immunoblotting, immunofluorescence 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 expression. 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.

P: 58

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

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

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

RESULTS: We observed 74 OHE events. The PHES was abnormal in 47 and predicted 31 OHE episodes among 14 patients (PPV = 29%, NPV of 75%, sens. 48%, spec. 65%). The CRT test was abnormal in 74/130 and predicted 54 OHE episodes among 23 patients (PPV = 31%, NPV = 78%, sens. 65%, spec. 46%). One or both tests were abnormal in 87/130 and predicted 60 OHE episodes among 27 patients (PPV = 31%, NPV = 81%, sens. 77%, spec. 40%). 43/130 had two normal tests but 8 experienced OHE and had 14 OHE-admissions.

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

P: 60

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 murine model of Type A HE that has a more protracted timeline of pathology.

METHODS: Male C57Bl6 mice were fed standard rodent chow enriched with 0.1% 3,5-dihydroxybenzyl-1,4-dihydrocollidine and 10% ammonium acetate (DDC + NH4). Neurobehavioral indices and neuromuscular deficits were assessed by open field test, rotarod, grip strength test and gait analysis. Serum, liver and brain tissue were analyzed for 13 amino acids, total bile acid content, and total ibe acid content were measured with colorimetric assays. Cerebral edema was assessed using the wet weight/dry weight method. Microglia activation was assessed by Iba1 immunochemistry. The expression of proinflammatory cytokines were assessed by qPCR and ELISA.

RESULTS: DDC + NH4 feeding caused significant neurological and neuromuscular deficits in every test performed commencing after 3–7 days of feeding. The liver damage observed was like a cholestatic...
hepatitis phenotype of drug-induced liver injury in humans, AST, ALT, alkaline phosphatase and total bilirubin were elevated. Histologically, there was evidence of intrahepatic cholestasis, drug-induced bile duct blockage, ductular reaction and immune cell infiltration, with low incidence of hepatocyte necrosis and little to no discernible fibrosis. Serum and cortical ammonia and total bile acid levels were elevated, and there was increased brain water content, indicating cerebral edema in DDC + NH4 fed mice. Furthermore, there was evidence of microglia activation and increased proinflammatory cytokine expression in the cortex of DDC + NH4 group compared to control diet-fed mice.

CONCLUSIONS: DDC + NH4 feeding generated key features of Type A HE, with a longer timeline of pathologic than the current models. With further characterization, this model may prove an effective and preferable model for pre-clinical studies to identify the pathogenesis or possible treatment options for Type A HE.

P: 61

Attenuation of Neurological Symptoms of Type C Hepatic Encephalopathy by Selective Ablation of Neuronal FXR Expression

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BACKGROUND: Hepatic encephalopathy (HE) describes the neurological deficits that result from liver impairment. Liver disease is associated with an increase of circulating bile acids that can cross the blood brain barrier and activate FXR receptors in neurons. We have previously demonstrated that aberrant bile acid signaling via activation of neuronal FXR contributes to HE pathogenesis in rodent models of acute liver failure. Furthermore, FXR is expressed in the brain with HE, but not in non-HE control samples. WT and FXR−/− mice generated by crossing Floxed FXR mice (FXRfl) with SNAP-25 cre recombinase mice. The resulting mice were designated FXRα/α (WT), FXR+, and FXRVO were treated with carbon tetrachloride (CCL4; 1 ml/kg) by oral gavage twice per week for 12 weeks. Neurobehavioral indices and neurometabolic data were assessed by open field test, motor coordination test and grip strength test and gait analysis. After 12 weeks, tissue was collected and liver damage was assessed by serum chemistry and H&E staining. Total bile acid content was assessed in the cortex and cerebellum using colorimetric assays. The expression of ASBT, FXR, and its downstream effector SHP was assessed by qPCR and immunofluorescence. Microglia activation was assessed by Iba1 immunofluorescence. The expression of proinflammatory cytokines was assayed by qPCR and ELISA. For parallel total bile acids, ASBT and FXR expression were assessed in brain tissue from cirrhotic patients with HE, compared to cirrhotics without HE and age- and gender-matched controls that had been collected and banked by the Australian Brain Bank Network.

RESULTS: Total bile acid content was elevated in the cortex and cerebellum in CCL4-treated WT mice and in cirrhotic patients with HE, compared to cirrhotics without HE and non-liver impaired controls. Furthermore, ASBT, FXR and SHP expression were increased in the frontal cortex of mice and humans with HE, but not in non-HE control samples. WT and FXR+/− mice treated with CCL4 had significant deficits observed in every neurobehavioral and neuromuscular test performed, as well as marked microglia activation and increased proinflammatory cytokine expression compared to vehicle-treated mice. These neurological deficits and neuroinflammation were attenuated in FXRVO mice after CCL4 treatment, even though liver damage was comparable in all genotypes of mice used.

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

P: 62

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

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

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

RESULTS: 5 patients (8–14 y) including 4 with CLD (2 girls), 1 with CPSS (1 girl), and 4 controls (10–14 y, 2 girls) underwent 1H-MRS. Causes of CLD: congenital disorder of glycosylation (1), progressive familial intrahepatic cholestasis type-2 (1), portal obliterative venopathy (1), autoimmune hepatitis (1). Mean plasma ammonium in patients was 26 umol/l, mean serum bilirubin was in normal range and mean platelet count was 201 G/L (59-346). The 3 patients with CLD showed scores in average or above average on Total Intellectual Quotient measures (WISC-IV). One of the 3 scored below average on the working memory sub-scale of the WISC-IV. One of the 3 scored below average on the Visuospatial sub-scale. The intelligence quotients were homogenous and above average for the 2 others patients. One of these 2 scored below average on 6/10 parameters on the Conners Continuous Performance Test, suggesting attention deficit. The other two were in range. The patient with CPSS displayed Total Intellectual Quotient below average (<1, 65 SD on the WISC-IV), with additional deficits (<1, 65 SD on the WISC-IV), in executive and attentional functioning as well as expressive and receptive language. 1H-MRS results: 13 metabolites were reliably quantified. Figure 1 illustrates the differences between CLD and CPSS: the expected increase of brain glutamine and decrease of brain osmolytes (inositol, taurine, total choline) together with...
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 neurochemical alterations as assessed by high resolution 1H-MRS. In CPSS, however, neurochemical 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).

P: 63

Drug-induced Hyperammonaemia: Data From VigiBase, the WHO Database
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BACKGROUND: Altered consciousness secondary to metabolic encephalopathies represents a major cause of ICU admission with favorable outcome when diagnosed and treated rapidly. Ammonia dosing is thus recommended in most textbooks in the absence of any diagnosis after etiological work-up encompassing biological sampling, cerebral imaging and EEG. Despite hyperammonaemia is most commonly secondary to liver diseases, postrheumatic shunts, inborn errors of metabolism, most likely cycle defects, microbial pullication 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, fluourouracil 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 (MedDRAv21.1) term (Preferred term [PT] level). The drugs considered in the analysis were those notified as suspected treatments. Drugs used to treat hyperammonaemia 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 (IC025) ≥ 0.05, an indicator value for disproportionate Bayesian reporting, was considered as causative of hyperammonaemia.

RESULTS: Among 19 438 165 ICSRs, 576 drugs were identified for the term “hyperammonaemia” [PT]. Six were excluded because they were used to treat hyperammonaemia or hepatic encephalopathy. Thus, 73 drugs had an NCBd 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.

P: 64

Multimodal Approach Including MR-spectroscopy for the Diagnosis of Minimal Hepatic Encephalopathy
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BACKGROUND: There is no gold-standard for the diagnosis of hepatic encephalopathy (HE) and in especial case of minimal HE (MHE) where the value of paraclinical examinations is debated. MR-spectroscopy has been proposed as a valuable diagnostic tool for the diagnosis of HE by showing increased glutamate/glutamine peak and decreased myo-inositol and choline peaks. However, access to MRI is difficult and few data on real life experience has been reported. We studied the interest of a multimodal approach combining clinical, neuropsychological, biological and MR-spectroscopy in the diagnosis of MHE.

METHODS: We conducted a retrospective study in a single tertiary university hospital in Paris, France, where all out-patients referred to a specific hepato-neurology consultation dedicated to the diagnostic of MHE underwent a clinical examination, psychometric tests (Critical Flicker Frequency, CFF, Psychometric Hepatic Encephalopathy Score–PHES), ammonium and cerebral MRS with spectroscopy (MRS). Patients were classified as having MHE or not by consensus between two experts.

RESULTS: We included 56 patients between February 2013 and April 2016. Median age was 57 years [49–63]. Forty-four (79%) had a cirrhosis (etiology: alcohol 35%, NASH 9%, viral 23%, alcoholic and non-alcoholic steatohepatitis 26%, other 7%) with a median MELD of 10 [7–12]. Twenty (21%) had non-cirrhotic portal hypertension (Budd-Chiari 33%, extra-hepatic portal hypertension 33%, idio-pathic portal hypertension 16%, portal agenesis 9% and nodular regenerative hyperplasia 9%). According to the experts, 57% had an MHE, whereas 43% hadn’t. Among the clinical information, only the presence of a postsysyctic shunt (TIPS or surgical) was associated with MHE. A venous ammonium >50 µmol/l, MRT T1 hyperintensity of the basal ganglia and an MRS HE profile suggesting of HE were all statistically associated with the diagnosis of MHE (P < 0.0001). The best diagnostic performance was achieved by combining MRS with either MRT T1 hyperintensity (AUC = 0.93) or ammonium (AUC = 0.91).

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

P: 65

Increased Levels of Xenobiotics in Plasma of Cirrhotic Patients With Neurological Symptoms, a Metabolic Study
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BACKGROUND: Encephalopathy is a classical complication of liver disease and/or portosystemic shunts. Its pathophysiology is not completely elucidated; mechanisms include the role of elevated ammonia levels in association with systemic inflammation. An impairment of blood-brain barrier (BBB) permeability is also hypothesized. Metabolomics enables to detect a wide range of metabolites without any a priori. In a recent metabolomic study including patients who underwent cerebrospinal fluid (CSF) collection, our group outlined that xenobiotics/drugs that usually are not able to cross BBB were retrieved in the CSF, suggesting a potential neurological toxicity of drugs. CSF collection is invasive. To describe the xenobiotics present in the plasma of cirrhotic patients, using the same metabolic 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-tandem mass spectrometry was performed and thereafter the metabolic fingerprints were compared to databases and between the different groups.

RESULTS: Plasma samples were obtained from 12 cirrhotic patients with encephalopathy (age 59 [40–68], MELD 20 [16–31], alcohol 58%), 13 cirrhotic patients without encephalopathy (age 56 [55–64], MILD 17 [14–29], alcohol 38%) and 9 healthy controls. Among 495 identified metabolites,
25 corresponded to xenobiotics or its derivatives. Fluoxetine was detected with a more than 200 fold increase, ammonium hydroxide 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, penicillamine 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: eugenol, isosorgenol (used in mouth bathing solution), triethanolamine (trolamine, 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.

**REFERENCES**


**P: 67**

**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. They adj

**METHODOLOGY: BDL-rats and sham-rats at 4 and 8-weeks post-BDL (n = 3/group/2-time-points) were used at each rat (n = 3 at 4-weeks and n = 3 at 8-weeks post-BDL, n = 5 Shams), seven slides/ rat were analyzed (distance between sections -250 microns). Morphometric measurements were performed using Sholl-analysis.**

**RESULTS:** Astrocytic activation is represented by the significant increase in GFAP+ cells at week4 post-BDL in the hippocampus (+47.5%) and cerebellum (+48.7%) vs SHAM (Figure 1a,b). Decrease in the processes intersection was observed already at week4 post-BDL (Figure 1c). The astrocytes were altered morphologically, showing shortening (hippocampus: week 4 - 13.3%, week 8 - 32.4%; cerebellum: week 4 - 17.3%, week 8 - 35.5%) and decreased number of processes (hippocampus: week 4 - 5.8%, week 8 - 18.77%; cerebellum: week 4 - 32.2%, week 8 - 41.5%) and processes intersections at week 8 post-BDL (hippocampus: ring:1 - 14.5%, ring 2 - 39%, ring 3 - 72.5%; cerebellum: ring:1 - 17.6%, ring 2 - 27.4%, ring 3 - 158.7%) 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**


**P: 68**

**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
**Fig. 1**

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

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

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

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**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±1.2μm² (p<0.00001). Two way-ANOVA: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, mean±SD.
with glutamine induces reactive-oxygen-species (ROS) generation associated with astrocyte impairment. 2,5 ROS play an important role in cellular signalling, synaptic-plasticity, learning and memory. In when in excess, they cause cellular damage. 6 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 in brain Asc in the hippocampus and cerebellum of BDL rats (model of CH). 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-SMR (Varian/Magneti-Sciences) using SPECIAL-sequence (TE = 2.8 ms). Ex-vivo-ESR: ESP300E (Bruker-BioSpin) was used for intracellular superoxide anion detection. Hippocampus/cerebellum were extracted at 6weeks post-BDL/sham-surgery (n = 9), incubated in medium with 10 mM-CM-cell-permeable spin-trap (Noyergn GmbH). Immunohistochemistry (IHC) GPX1 (antioxidative enzyme) staining was performed (n = 6).

RESULTS: The increase in plasma NH4+ and bilirubin confirmed the presence of chronic liver disease. A – 80% increase in brain glutamine was measured at week 6, while Asc showed a stronger decrease in cerebellum (~32% at week 6, P < 0.001) (Figure 1a). ESR revealed differences in redox-state between the two brain regions (~31% higher in cerebellum, P < 0.004) (Figure 1b). However, the relative change in both regions between BDL and sham was similar (~42%). The significant increase of hippocampal/cerebellar OS in BDL (P < 0.01, P < 0.001) corroborate the 1H-MRS findings of decreased Asc concentrations (Figure 1a). IHC with GPX1-enzyme revealed an increased activity in Purkinje and granular-cell-layer of BDL cerebellum (Figure 1c). Purkinje-cells also showed shrinking soma (BDL: 8.04 ± 18 μm2, sham: 12.5 ± 1.2 μm2, P < 0.0001). Elevated GPX1 in cerebellum suggests that GSH-synthesis may increase (confirmed by increased GSH in 1H MRS, Figure 1a) in response to OS-related injury. Elevated OS might suggest that ROS could lead to brain functions disruption. 10,12

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

REFERENCES
BACKGROUND: 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 sodium (spontaneous or induced by an aquaretic) leads to an improvement in 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

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BACKGROUND: Astrocyte swelling and brain edema are major complications of severe liver failure. Ammonia plays a major role in the development of astrocyte swelling/brain edema in this condition. However, current therapies have not thus far improved the outcome of liver failure induced astrocyte swelling/brain edema. Since acetate has been shown to have neuroprotective effect in other neurological conditions, likely though 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 glycerol triacistrate (GTA), an acetate precursor, which is known to increase circulating, as well as tissue levels of acetate, alleviates the brain edema induced by the liver toxin thioacetamide (TAA).

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

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

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

Cholestasis Decreases Dendritic Spine Density in a Rat Hippocampal Organotypic Culture

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BACKGROUND: Executive functioning impairment in children with cholestatic liver disease is increasingly recognized. Injury to developing neuronal networks could be an underlying mechanism. Given that the CSF of rat pups following bile duct ligation is highly concentrated in ammonia, murine cholestasis models show significant increases in ammonia. Given that the CSF of rat pups following bile duct ligation is highly concentrated in ammonia, murine cholestasis models show significant increases in ammonia. We hypothesized that cholestasis may significantly alter dendritic spine density in developing neuronal networks. In order to test this hypothesis, we transplanted cholestatic organotypic hippocampal slices into normal rats and vice versa.

METHODS: Transverse hippocampal organotypic slice (400 µm thick) were harvested from 6-day-old Wistar rats. They were maintained for 15 days in a CO2-incubator (33°C). pc-DNA3.1-GFP plasmid bidirectional transfection was performed 7 days after harvesting. 3 days following transfection, control medium or experimental medium containing 100 mM o-methylglucaric acid and 2.5 mM ammonium was added to the culture (day 0 of exposure, MIX condition). Confocal microscopy using imaged was used for to manually count CA1 pyramidal neuron dendritic spines as proxies for excitatory synapses. Static analysis quantified dendritic spines density each day. Dynamic analysis quantified dendritic spines turnover (loss and neo-formation) for each 24 h time-window. Statistical analysis was conducted using Prism software for multiple t-test or mixed-effect ANOVA.

RESULTS: Static analysis showed a bifurcating profile in MIX condition. During early phase (first 3 days of exposure), we observed >50% decrease in dendritic spine density compared to control (f Figure 1, P < 0.001). On days 3 to 4, spine density recovered to reach control value. Dynamic analysis showed 15% loss in dendritic spines stability during the early phase of exposure to MIX condition, compared to controls, with comparable low rates of spine turnover. During the late phase of MIX exposure, spine turnover increased significantly in favor of spine neo-formation: spine neo-formation was 10 times higher (0.280 vs 0.023 spines/µm3, P = 0.033) than controls, while spine loss was 6 times higher in neurons exposed to MIX (0.154 vs 0.026 spines/µm3, P = 0.0026) than controls.

CONCLUSIONS: We demonstrate here that mimicking cholestasis ex vivo leads to a biphasic response in spine density of rat hippocampal CA1 pyramidal neurons. Spine density decreases during...
**Reversible and Irreversible Neurological Complications in Hepatic Encephalopathy**

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**ABSTRACT:** Cerebral edema and associated increase in intracranial pressure, along with brain herniation 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)-treated rat model of acute and chronic HE. Accordingly, rats were treated with the liver toxin TAA and brain edema, neurobehavioral, cognitive and motor deficits were measured.

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

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

**P: 77**

**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 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)-treated 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.

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Support: VA Merit review, AASLD/ALF.

**P: 78**

**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

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**Fig:** Hippocampal pyramidal neurons dendritic spines density, ***p < 0.001**

![Graph](image-url)
P: 79
Central Inhibition of IGFBP3 Attenuates Symptoms of Hepatic Encephalopathy in a Mouse Model of Acute Liver Failure

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BACKGROUND: Insulin-like growth factor binding protein 3 (IGFBP3) has a strong binding affinity for IGF proteins and can inhibit the function of IGF by preventing interaction with its receptor. In addition, IGFBP3 can exert IGF-independent effects via direct interaction with a putative IGFBP receptor. Little is known about the function of IGFBP3 in the brain, outside of a role in brain cancer development. We have recently demonstrated that IGFBP3 expression is suppressed in the frontal cortex in a number of rodent models of hepatic encephalopathy (HE) and central administration of recombinant IGFBP3 attenuates the neurological complications. However, the role of IGFBP3 in the pathogenesis of HE is unknown and is the aim of this study.

METHODS: C57Bl/6 mice injected with ammonium acetate (AOM) to induce acute liver failure and HE. In parallel, mice were given an intracerebroventricular infusion of the IGFBP3 inhibitor, NR31772 for 3 days prior to AOM injection. Cognitive impairment was monitored by reflex response assessment at various time points and neuromuscular deficits were assessed using a grip strength meter. Liver damage was determined by H&E and stain and serum chemistry. The expression of IGFBP3 and IGF1 was assessed in the cortical pCGR, EIA and immunofluorescence using NeuN and a-tubulin and glial fibrillary acidic protein, along with increased levels of aggregated nuclear protein lamin a/c in the thionoacetic acid-induced rat model of CHE. Further, we identified reduced levels of neuronal proteins, PSD95, synaptophysin, and NMDA-r1. Moreover, synaptic density and dendritic complexity are reduced post-CLF. Since elevated blood/brain ammonia levels have been strongly implicated in the pathogenesis of CHE, while exposure of cultured astrocytes to ammonia was shown to develop AT2A, we utilized this in vitro system to delineate mechanisms by which ammonia contributes to the development of AT2A. We found increased levels of IGF1, aggregated nuclear protein lamin a/c, and IGF1 in the cortex by qPCR, EIA and immunohistochemistry and by ELISA. AT2A was analyzed by histopathology.

RESULTS: Seventy-six (33.6%) of the 226 patients had abnormal UK PHES scores. Variation in the scoring of the LTT test (German, Spanish and Italian versions) resulted in a minor reduction in the number of abnormal results (73 (32%)). Add-in and subtraction models for the independent correction factors - age, sex, ethnicity, alcohol consumption, years/education were associated with changes of -11% to +9.8% and +2.4 to -8.8% respectively, in the proportion of abnormal result; ethnicity and age had the greatest effects. Adding interaction terms for the correction factors marginally increased the number of abnormal results to 84 (37.2%). Changing the final score summation from Z-scores to integrated scores significantly increased the number of abnormal tests to 100 (44.2%) P = 0.026.

CONCLUSIONS: The major factor affecting the proportion of abnormal PHES results is the method used for final summation of the scores. Integration of the scores does not allow for the exact application of thresholds and its use should perhaps be reconsidered.

P: 81
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. Recently, there has been interesting the possibility that the susceptibility to develop HE is, at least in part, genetically determined. In 2017, Gils-Gómez et al. Hepatology 2017,66(Suppl 1):S144 reported significant associations between variants in nine candidate genes and the presence of overt HE in 400 patients included in the CLIF consortium cross-sectional study. In this study overt HE was diagnosed using the West Haven criteria, while acute on chronic liver failure (ACLF) was diagnosed using the CLIF-OH score. The aim of the present study was to replicate these findings in participants in the STOPAH alcoholic hepatitis treatment trial.

METHODS: Genomic DNA was available in 731 participants in the STOPAH trial. Overt HE was diagnosed using the West Haven criteria, ACLF was diagnosed using the CLIF-OH score. Data on six of the nine SNP associated with overt HE and/or ACLF in the Spanish study were identified in the STOPAH GWAS database. Genotypic association analyses were undertaken for each of the genetic variants in the entire population and in subgroups defined by the presence of overt HE and/or ACLF.

RESULTS: A total of 199 (27.2%) of the 731 STOPAH participants had overt HE on admission, while 193 (26.3%) had ACLF. Patients were classified as follows: HE and ACLF (n = 61), HE but no ACLF (138), ACLF but no HE (n = 132), no MCLF and no HE (n = 400). Only one significant association was identified var. rs7528949 in SLC1A2 in participants with overt HE but without ACLF (Table 1); however, the significance of this association was lost when the data were corrected for multiple testing.

CONCLUSIONS: The previously reported genetic associations with overt HE were not replicated in the present study. The number of participants was almost double that in the Spanish study but the proportions of patients with HE and ACLF were similar. Not all of the reported SNPs were available but at least two SNPs were tested for association in each patient subgroup. Further large case-control studies and meta-analyses of existing data are needed.

P: 82
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). The gut is a major source of ammonia production that contributes to systemic hyperammonemia in CLD and HE and remains the primary therapeutic target for lowering circulating ammonia. As a therapeutic strategy, Escherichia coli Nissle 1917, a well characterized probiotic, was genetically modified to consume and convert ammonia to arginine (SYNARG), and its administration to thioacetamide-treated mice resulted in a significant reduction of ammonia levels. SYNARG was further modified to synthesize butyrate interactions between the corrections variables; (a) the scoring of the line tracing test (LTT) and (ii) the final summation of the component scores. The aim of this study was to produce a series of models to determine the influence of these variables on the performance of the PHES test.

METHODS: PHES testing was undertaken in 324 permanent UK residents aged > 18 years, who spoke English, and were generally healthy. A UK PHES model was constructed as follows: (i) a reciprocal model for the LTT time/error relationship was devised; (ii) univariate/multivariate analyses identified significant correction factors for the individual test scores, without applying interaction terms; and (iii) each corrected test score was transformed to a Z-Score and then summed. The final PHES score was expressed as a Z-Score, values below ~2.0 were considered abnormal. The effects of changing the basic PHES model by adding in interaction terms, changing the LTT scoring system and the final summation method were examined by applying the models to PHES data collected in 226 patients with cirrhosis.

RESULTS: Seventy-six (33.6%) of the 226 patients had abnormal UK PHES scores. Variation in the scoring of the LTT test (German, Spanish and Italian versions) resulted in a minor reduction in the number of abnormal results (73 (32%)). Add-in and subtraction models for the independent correction factors - age, sex, ethnicity, alcohol consumption, years/education were associated with changes of -11% to +9.8% and +2.4 to -8.8% respectively, in the proportion of abnormal result; ethnicity and age had the greatest effects. Adding interaction terms for the correction factors marginally increased the number of abnormal results to 84 (37.2%). Changing the final score summation from Z-scores to integrated scores significantly increased the number of abnormal tests to 100 (44.2%) P = 0.026.

CONCLUSIONS: The major factor affecting the proportion of abnormal PHES results is the method used for final summation of the scores. Integration of the scores does not allow for the exact application of thresholds and its use should perhaps be reconsidered.

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Obesity Accelerates and Exacerbates Neurological Impairments Associated to Hepatic Encephalopathy in Chronic Liver Disease

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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. 3-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 at 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 5 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. Hypolocomotion 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 increase 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.

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.

P: 83

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