View this email in your browser

Liver Digest

A weekly update of PLRC happenings

July 10, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Mordechai Rabinovitz

In this issue

PLRC Meet & Greet

To celebrate our first major success in obtaining extramural funding and to provide an opportunity to further understand the organization and functioning of the PLRC, we will organize an evening reception in the later part of August. Please keep an eye out for this invitation.

In the meantime, if there are any questions or comments, please feel free to contact us.

Faculty Highlights

Original Article:

Toney NA, Bell MJ, Belle SH, Hardison RM, Rodriguez-Baez N, Loomes KM, **Vodovotz Y**, **Zamora R**, **Squires RH**; Pediatric Acute Liver Failure Study Group. Hepatic Encephalopathy in Children with Acute Liver Failure - Utility of Serum Neuromarkers. J Pediatr Gastroenterol Nutr. 2019 Apr 15. doi: 10.1097/MPG.0000000000002351. [Epub ahead of print] PubMed PMID: 31058776.

ABSTRACT

BACKGROUND: Pediatric acute liver failure (PALF) is a public heath burden, often requiring prolonged hospitalization and liver transplantation. Hepatic encephalopathy (HE) is a complication of PALF with limited diagnostic tools to predict outcomes. Serum neurological markers (neuron-specific enolase, S100β, and myelin basic protein) can be elevated in traumatic or ischemic brain injury. We hypothesized that these neuromarkers would be associated with the development of HE in PALF.

METHODS: PALF study participants enrolled between May 2012 and December 2014 by 12 participating centers were the subjects of this analysis. Daily HE assessments were determined by study investigators. Neurological and inflammatory markers were measured using enzyme-linked immunosorbent assay and MILLIPLEX techniques, respectively. To model encephalopathy, these markers were log2 transformed and individually examined for association with HE using a generalized linear mixed model with a logit link and random intercept.

RESULTS: Eighty-two children had neurological and inflammatory marker levels and HE assessments recorded, with the majority having assessments for 3 days during their illness. An indeterminate diagnosis (29%) was most common and the median age was 2.9 years. Significant associations were observed for HE with

S100β (odds ratio 1.16, 95% confidence interval [1.03-1.29], P=0.04) and IL-6 (odds ratio 1.24 [1.11-1.38], P=0.006).

CONCLUSIONS: Serum S100β and IL-6 are associated with HE in children with PALF. Measuring these markers may assist in assessing neurological injury in PALF, impacting clinical decisions.

For full text, please **click here**.

Original Article:
Kuo SZ, Ahmad M, **Dunn MA**, Montano-Loza AJ, Carey EJ, Lin S, Moghe A, Chen HW, Ebadi M, Lai JC. Sarcopenia Predicts Posttransplant Mortality in Acutely Ill Men Undergoing Urgent Evaluation and Liver Transplantation. Transplantation. 2019 Apr 8. doi: 10.1097/TP.0000000000002741. [Epub ahead of print] PubMed PMID: 30985575.

ABSTRACT
BACKGROUND: We examined the association between sarcopenia and posttransplant mortality in acutely ill inpatients with cirrhosis who underwent urgent liver transplantation.

METHODS: Included were inpatients at 4 centers who were urgently listed as non-Status 1 and transplanted from 2005-17 with an abdominal computed tomography scan <90 days prior. Skeletal muscle index (SMI) = total skeletal muscle cross sectional area the L3 vertebral level, normalized to height. Cox regression associated SMI with posttransplant mortality. Optimal search identified SMI cutoffs to detect survival.

RESULTS: Of 126 inpatients: 63% were male, MELD-Na was 32, and follow up was 5.1 years. Among men: 23% died. Median SMI was lower in men who died versus survived (45 versus 51 cm/m). SMI was associated with posttransplant mortality (HR=0.96 per cm/m, 95%CI 0.92-0.99). Patients with SMI ≤ versus >48 cm/m experienced higher rates of death at 1- (86% versus 95%) and 3-years (73% versus 95%) (logrank P = 0.01). In MELD-adjusted analysis, sarcopenia was strongly associated with posttransplant mortality (HR=4.39, 95%CI 1.49-12.97).Among women: 35% died. Median SMI was similar in women who died versus survived (45 versus 44 cm/m). SMI was not associated with posttransplant mortality (HR=1.02, 95%CI 0.96-1.09). Optimal search did not identify any SMI cutoff that predicted posttransplant mortality.

CONCLUSION: Among patients who underwent urgent inpatient evaluation and liver transplantation, we identified an SMI cut-off of 48 cm/m to predict posttransplant mortality in men. Our data support the use of SMI as a tool to capture the impact of muscle depletion on posttransplant mortality in acutely ill men with cirrhosis undergoing urgent liver transplantation.

For full text, please **click here**.

Original Article:

An Y, Wang P, Xu P, Tung HC, Xie Y, Kirisci L, Xu M, Ren S, Tian X, **Ma X**, **Xie W**. An Unexpected Role of Cholesterol Sulfotransferase and its Regulation in Sensitizing Mice to Acetaminophen-Induced Liver Injury. Mol Pharmacol. 2019 Jun;95(6):597-605. doi: 10.1124/mol.118.114819. Epub 2019 Apr 3. PubMed PMID: 30944208.

ABSTRACT

Overdose of acetaminophen (APAP) is the leading cause of acute liver failure (ALF) in the United States. The sulfotransferase-mediated sulfation of APAP is widely believed to be a protective mechanism to attenuate the hepatotoxicity of APAP. The cholesterol sulfotransferase SULT2B1b is best known for its activity in catalyzing the sulfoconjugation of cholesterol to synthesize cholesterol sulfate. SULT2B1b can be transcriptionally and positively regulated by the hepatic nuclear factor 4α (HNF4α). In this study, we uncovered an unexpected role for SULT2B1b in APAP toxicity. Hepatic overexpression of SULT2B1b sensitized mice to APAP-induced liver injury, whereas ablation of the Sult2B1b gene in mice conferred resistance to the APAP hepatotoxicity. Consistent with the notion that Sult2B1b is a transcriptional target of HNF4α, overexpression of HNF4α sensitized mice or primary hepatocytes to APAP-induced hepatotoxicity in a Sult2B1b-dependent manner. We conclude that the HNF4α-SULT2B1b axis has a unique role in APAP-induced acute liver injury, and SULT2B1b induction might be a risk factor for APAP hepatotoxicity.

For full text, please **click here**.

Our mailing address is:
Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261