Liver Digest

A weekly update of PLRC happenings

April 11, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Lawrence Vernetti

In this issue

This Week's Seminar

Special Seminar:

Wednesday, April 17, 2019

12:00-1:00 pm

West Wing Auditorium - Shadyside Hospital

Mitesh Borad, MD

Associate Professor of Medicine

Mayo Clinic College of Medicine and Science

Phoenix, Arizona

Clinical Translation of Oncolytic Virotherapy

Lunch will be provided.

Liver-Themed Gut Club - May 2

Dr. Fasiha Kanwal, the division chief at Baylor, will speak at the May 2, 2019 Pittsburgh Gut Club accredited dinner/lecture series on "The Changing Epidemiology of Liver Cancer."

Liver-related clinical and research trainees are invited to attend the lecture with fee-waived registration. All faculty are invited to attend as well but are required to pay to attend. But, they welcome your trainees as fee-waived participants.

To register for this event, please complete the registration form found in the brochure available on the here (trainees mark "fee waived" in the payment section), and scan (joj2@pitt.edu) or fax (412-578-9537) it to Joy Merusi by April 15th.

Faculty Highlights

Editorial:

Bataller R, **Arteel GE**, Moreno C, Shah V. Alcohol-related liver disease: Time for action. J Hepatol. 2019 Feb;70(2):221-222. doi: 10.1016/j.jhep.2018.12.007. PubMed PMID: 30658723.

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

Original Article:

Rachakonda V, Argemi J, **Borhani AA**, **Bataller R**, Tevar A, **Behari J**. Reduced Serum Sphingolipids Constitute a Molecular Signature of Malnutrition in Hospitalized Patients With Decompensated Cirrhosis. Clin Transl Gastroenterol. 2019 Mar;10(3):e00013. PMID: 30908309

ABSTRACT

INTRODUCTION: Malnutrition is a leading cause of morbidity and mortality in cirrhosis. Although multiple noninvasive measures of nutritional status have been studied, no consensus exists for early identification of malnutrition in cirrhosis. Serum metabolomics offers a novel approach for identifying biomarkers in multiple disease states. To characterize alterations in metabolic pathways associated with malnutrition in hospitalized cirrhotic patients and to identify biomarkers for disease prognosis.

METHODS: In this cross-sectional, observational cohort study, 51 hospitalized cirrhotic patients were classified as malnourished (42.3%) or nourished (57.7%) based on low mid-arm muscle circumference and dominant handgrip strength. Anthropometric measurements and computed tomography body composition analysis were performed. Serum was collected after overnight fasting for unbiased metabolomics analysis.

RESULTS: Malnourished cirrhotic patients exhibited mild reductions in skeletal muscle index, with more marked reductions in visceral fat index. Seventy-one biochemicals were significantly altered in malnourished subjects. The serum metabolite profile was significantly different between nourished and malnourished cirrhotic patients. Pathway analysis demonstrated that only sphingolipid metabolic pathways were significantly enriched in altered metabolites.

Hierarchical clustering revealed that sphingolipid metabolites clustered into nourished and malnourished cohorts. Spearman analysis demonstrated multiple statistically significant correlations between sphingolipid species and Model for End-Stage Liver Disease-Sodium. Using logistic regression, we identified 8 sphingolipids that were significantly associated with malnutrition after controlling for Model for End-Stage Liver Disease-Sodium, age, and gender.

CONCLUSIONS: Malnutrition in hospitalized cirrhotic patients is characterized by reductions in multiple sphingolipid species. Dysregulated sphingolipid metabolism may be involved in the pathophysiology of malnutrition in cirrhosis and potentially serve as a biomarker of nutritional status in this population.

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

Dr. Paul Monga's presentation highlighted at Annual Experimental Biology Meeting

Tomorrow's Highlights: Monday, April 8

Liver Workshop – The Promiscuous Ways of Prometheus: Liver Repair and Beyond

8:30–11:30 a.m. | Convention Center, Room W105B

Speakers will describe the current state of our understanding of the cellular plasticity of the liver and the molecular pathways and factors that drive generation of new cells from stem cells and transdifferentiation of mature cell types.

Original Article:

Berauer JP, Mezina AI, Okou DT, Sabo A, Hegde MR, Chopra P, Perlmutter DH, Bull LN, Thompson RJ, Loomes KM, Spinner NB, Rajagopalan R, Guthery SL, Moore B, Shneider BL, Magee JC, Kamath BM, Molleston JP, Bezerra JA, Murray KF, Alonso EM,

Rosenthal P, **Squires RH**, Sherker AH, Sokol RJ, Wang KS, for the Childhood Liver Disease Research Network (ChiLDReN), and Karpen SJ. Identification of PKD1L1 Gene Variants in Children with the Biliary Atresia Splenic Malformation Syndrome. Hepatology. Published ahead of Press. (PMID: 30664273)

ABSTRACT
Biliary atresia (BA) is the most common cause of end-stage liver disease in children and the primary indication for pediatric liver transplantation, yet underlying etiologies remain unknown. Approximately 10% of infants affected by BA exhibit various laterality defects (heterotaxy) including splenic abnormalities and complex cardiac malformations-a distinctive subgroup commonly referred to as the biliary atresia splenic malformation (BASM) syndrome. We hypothesized that genetic factors linking laterality features with the etiopathogenesis of BA in BASM patients could be identified through whole-exome sequencing (WES) of an affected cohort. DNA specimens from 67 BASM subjects, including 58 patient-parent trios, from the National Institute of Diabetes and Digestive and Kidney Diseases-supported Childhood Liver Disease Research Network (ChiLDReN) underwent WES. Candidate gene variants derived from a prespecified set of 2,016 genes associated with ciliary dysgenesis and/or dysfunction or cholestasis were prioritized according to pathogenicity, population frequency, and mode of inheritance. Five BASM subjects harbored rare and potentially deleterious biallelic variants in polycystic kidney disease 1 like 1 (PKD1L1), a gene associated with ciliary calcium signaling and embryonic laterality determination in fish, mice, and humans. Heterozygous PKD1L1 variants were found in 3 additional subjects. Immunohistochemical analysis of liver from the one BASM subject available revealed decreased PKD1L1 expression in bile duct epithelium when compared to normal livers and livers affected by other noncholestatic diseases. Conclusion: WES identified biallelic and heterozygous PKD1L1 variants of interest in 8 BASM subjects from the ChiLDReN data set; the dual roles for PKD1L1 in laterality determination and ciliary function suggest that PKD1L1 is a biologically plausible, cholangiocyte-expressed candidate gene for the BASM syndrome.

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

Original Article:
Wilson GC, Lluis N, **Nalesnik MA**, Nassar A, Serrano T, Ramos E, Torbenson M, Asbun HJ, **Geller DA**. Hepatic Angiosarcoma: A Multi-institutional, International Experience with 44 Cases. Ann Surg Oncol. 2019 Feb;26(2):576-582. doi: 10.1245/s10434-018-7062-9. Epub 2018 Nov 19. PubMed PMID: 30456677.

ABSTRACT

BACKGROUND: Hepatic angiosarcoma is a rare primary liver tumor. The aim of this current study was to evaluate the presentation and treatment outcomes in a modern cohort.

METHODS: This was a retrospective, multi-institutional, observational study of patients with histopathologic diagnoses of primary hepatic angiosarcoma from four institutions. Clinicopathologic characteristics, treatments, and patient outcomes were examined.

RESULTS: Forty-four patients with hepatic angiosarcoma were identified. Patients were predominantly Caucasian and presented at a median age of 63.7 years; 81.4% of patients had bilobar disease and 37.2% had metastatic disease at the time of presentation. Only 10 patients underwent surgical resection. Median overall survival for the entire cohort was 5.8 months (interquartile range 1.9-16.4), and 1-, 3-, and 5-year actual survival was 30.0%, 8.1%, and 5.6%, respectively. There were only two 5-year survivors, both of whom presented with localized disease and underwent curative resection.

CONCLUSION: The prognosis for hepatic angiosarcoma remains quite poor. Surgical resection for localized disease results in the best outcomes. Unfortunately, current imaging modalities are often non- diagnostic, and most patients are unresectable at the time of presentation

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

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