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Liver Digest

A weekly update of PLRC happenings

April 25, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

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Featured Faculty - Dr. Donna Stolz

In this issue

Next Week's Seminars

Liver Seminar

Wed, 05/01/2019

12:00 to 1:00 pm

1104 Scaife

Seth Karp, MD

Chair, Section of Surgical Sciences

Director, Vanderbilt Transplant Center

Vanderbilt University Medical Center

Hepatocyte Function in Maintaining Homeostasis and Recreating Liver Microstructure During and After Injury

This activity has been approved for AMA PRA Category 1 Credit(s)™

Pizza will be provided.

Faculty Highlights

Short Communication:

Johansen L, Haller W, Thyagarajan M, Kelly D, **McKiernan P.** Hepatic Lesions Associated with McCune Albright Syndrome. Journal of Pediatric Gastroenterology and Nutrition. 68(4):e54–e57, APR 2019. DOI: 10.1097/MPG.0000000000002266, PMID: 30628989. Publication Date: 2019/04/01

ABSTRACT
McCune-Albright syndrome (MAS) results from a GNAS gene mutation. It is associated with café au lait macules, fibrous dysplasia, and several endocrinopathies to include gonadotropin-independent precocious puberty, growth hormone excess, Cushing syndrome, thyroid disease, and renal phosphate wasting. It is recognized to be a rare cause of neonatal cholestasis. We describe the hepatic outcome of 3 children with MAS referred to a single national liver unit. All presented with high gamma-glutamyl transpeptidase cholestasis and hepatitis. Cholestasis resolved by 1 year; but hepatic inflammation persisted, and 2 children developed progressive atypical focal nodular hyperplasia and 1 developed hepatoblastoma. This the first reported malignant hepatic lesion associated with MAS. MAS should be considered part of the differential diagnosis of neonatal cholestasis and affected children should be closely monitored for the development of hepatic lesions with regular liver ultrasound and alpha fetoprotein level.

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

Multidisciplinary Report:

Freeman AJ, Sellers ZM, **Mazariegos G**, Kelly A, Saiman L, Mallory G, Ling SC, Narkewicz MR, Leung DH. A multi-disciplinary approach to pre and post-transplant management of cystic fibrosis associated liver disease. Liver Transpl. 2019 Jan 29. doi: 10.1002/lt.25421. [Epub ahead of print] PubMed PMID: 30697907.

ABSTRACT
Approximately 5%-10% of patients with cystic fibrosis (CF) will develop advanced liver disease with portal hypertension, representing the third leading cause of death among patients with CF. Cystic fibrosis with advanced liver disease and portal

hypertension (CFLD) represents the most significant risk to patient mortality, second only to pulmonary or lung transplant complications in patients with CF. Currently, there is no medical therapy to treat or reverse CFLD. Liver transplantation (LT) in patients with CFLD with portal hypertension confers a significant survival advantage over those who do not receive LT, although the timing in which to optimize this benefit is unclear. Despite the value and efficacy of LT in selected patients with CFLD, established clinical criteria outlining indications and timing for LT as well as disease-specific transplant considerations are notably absent. The goal of this comprehensive and multidisciplinary report is to present recommendations on the unique CF-specific pre- and post-LT management issues clinicians should consider and will face.

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

Original Article:

Shah ND, Ventura-Cots M, Abraldes JG, Alboraie M, Alfadhli A, Argemi J, Badia-Aranda E, Soler EA, Barritt AS 4th, Bessone F, Biryukova M, Carrilho FJ, Fernández MC, Guiridi ZD, El Kassas M, Eng-Kiong T, Farias A, George J, Gui W, Thurairajah PH, Hsiang JC, Husić-Selimovic A, Isakov V, Karoney M, Kim W, Kluwe J, Kochhar R, Dhaka N, Costa PM, Nabeshima MA, Ono SK, Reis D, Rodil A, Domech CR, Sáez-Royuela F, Scheurich C, Siow W, Sivac-Burina N, Dos Santos Traquino ES, Some F, Spreckic S, Tan S, Vorobioff J, Wandera A, Wu P, Yakoub M, Yang L, Yu Y, Zahiragic N, Zhang C, Cortez-Pinto H, **Bataller R.** Alcohol-related Liver Disease is Rarely Detected at Early Stages Compared With Liver Diseases of Other Etiologies Worldwide. Clin Gastroenterol Hepatol. 2019 Jan 29. pii: S1542-3565(19)30073-4. doi: 10.1016/j.cgh.2019.01.026. [Epub ahead of print] PubMed PMID: 30708110.

ABSTRACT

BACKGROUND & AIMS: Despite recent advances in treatment of viral hepatitis, liver-related mortality is high, possibly owing to the large burden of advanced alcohol-related liver disease (ALD). We investigated whether patients with ALD are initially seen at later stages of disease development than patients with hepatitis C virus (HCV) infection or other etiologies.

METHODS: We performed a cross-sectional study of 3453 consecutive patients with either early or advanced liver disease (1699 patients with early and 1754 with advanced liver disease) seen at 17 tertiary care liver or gastrointestinal units worldwide, from August 2015 through March 2017. We collected anthropometric, etiology, and clinical information, as well as and model for end-stage liver disease scores. We used unconditional logistic regression to estimate the odds ratios for evaluation at late stages of the disease progression.

RESULTS: Of the patients analyzed, 81% had 1 etiology of liver disease and 17% had 2 etiologies of liver disease. Of patients seen at early stages for a single etiology, 31% had HCV infection, 21% had hepatitis B virus infection, and 17% had nonalcoholic fatty liver disease, whereas only 3.8% had ALD. In contrast, 29% of patients seen for advanced disease had ALD. Patients with ALD were more likely to be seen at specialized centers, with advanced-stage disease, compared with patients with HCV-associated liver disease (odds ratio, 14.1; 95% CI, 10.5-18.9; $P < .001$). Of patients with 2 etiologies of liver disease, excess alcohol use was associated with 50% of cases. These patients had significantly more visits to health care providers, with more advanced disease, compared with patients without excess alcohol use. The mean model for end-stage liver disease score for patients with advanced ALD (score, 16) was higher than for patients with advanced liver disease not associated with excess alcohol use (score, 13) ($P < .01$).

CONCLUSIONS: In a cross-sectional analysis of patients with liver disease worldwide, we found that patients with ALD are seen with more advanced-stage disease than patients with HCV-associated liver disease. Of patients with 2 etiologies of liver disease, excess alcohol use was associated with 50% of cases. Early detection and referral programs are needed for patients with ALD worldwide.

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

Original Article:
Liya Chen, Anna L. Lang, Gavin D. Poff, Wen-Xing Ding, **Juliane I. Beier**. Vinyl chloride-induced interaction of nonalcoholic and toxicant-associated steatohepatitis: Protection by the ALDH2 activator Alda-1. Redox Biology, Volume 24, June 2019, 101205.

ABSTRACT
Vinyl chloride (VC), an abundant environmental contaminant causes steatohepatitis at high levels, but is considered safe at lower (i.e., sub-OSHA) levels. However, we have previously shown that even lower VC levels exacerbate experimental nonalcoholic fatty liver disease (NAFLD) caused by high-fat diet (HFD). Mitochondrial oxidative injury and subsequent metabolic dysfunction appeared to play key roles in mediating this interaction. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) serves as a key line of defense against endogenous and exogenous reactive aldehydes. The current study therefore tests the hypothesis that allosteric activation of ALDH2 with Alda-1 will protect against VC-enhanced NAFLD. Mice were exposed to low VC concentrations (<1 ppm), or room air for 6 h/day, 5 days/week for 12 weeks, while on HFD or low-fat control diet (LFD). Some mice received Alda-1 (20 mg/kg i.p., 3 × /week) for the last 3 weeks of diet/VC exposure. Indices of liver injury, oxidative stress, metabolic and mitochondrial (dys)function were

measured. As observed previously, low-dose VC did not cause liver injury in control mice; while liver injury caused by HFD was enhanced by VC. VC decreased hepatic ALDH2 activity of mice fed HFD. Alda-1 attenuated oxidative stress, liver injury, and dysmetabolism in mice exposed to HFD+VC under these conditions. Importantly, alterations in mitochondrial function caused by VC and HFD were diminished by Alda-1. Previous studies have indicated that liver injury caused by HFD is mediated, at least in part, by enhanced mitochondrial autophagy (mitophagy). Here, Alda-1 suppressed PINK1/PARKIN-mediated mitophagy. Taken together, these results support the hypothesis that ALDH2 is a critical defense against mitochondrial injury caused by VC in experimental NAFLD. The ALDH2 activator Alda-1 conferred protection against liver damage under these conditions, most likely via increasing clearance of aldehydes and preserving mitochondrial respiratory function.

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

Original Article:

Thapa D, Wu K, Stoner MW, Xie B, Zhang M, Manning JR, Lu Z, Li JH, Chen Y, Gucek M, Playford MP, Mehta NN, Harmon D, **O'Doherty RM**, **Jurczak MJ**, Sack MN, Scott I. The protein acetylase GCN5L1 modulates hepatic fatty acid oxidation activity via acetylation of the mitochondrial β-oxidation enzyme HADHA. J Biol Chem. 2018 Nov 16;293(46):17676-17684. doi: 10.1074/jbc.AC118.005462. Epub 2018 Oct 15. PubMed PMID: 30323061; PubMed Central PMCID: PMC6240879.

ABSTRACT

Sirtuin 3 (SIRT3) deacetylates and activates several mitochondrial fatty acid oxidation enzymes in the liver. Here, we investigated whether the protein acetylase GCN5 general control of amino acid synthesis 5-like 1 (GCN5L1), previously shown to oppose SIRT3

activity, is involved in the regulation of hepatic fatty acid oxidation. We show that GCN5L1 abundance is significantly up-regulated in response to an acute high-fat diet (HFD). Transgenic GCN5L1 overexpression in the mouse liver increased protein acetylation levels, and proteomic detection of specific lysine residues identified numerous sites that are co-regulated by GCN5L1 and SIRT3. We analyzed several fatty acid oxidation proteins identified by the proteomic screen and found that hyperacetylation of hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit α (HADHA) correlates with increased GCN5L1 levels. Stable GCN5L1 knockdown in HepG2 cells reduced HADHA acetylation and increased activities of fatty acid oxidation enzymes. Mice with a liver-specific deletion of GCN5L1 were protected from hepatic lipid accumulation following a chronic HFD and did not exhibit hyperacetylation of HADHA compared with WT controls. Finally, we found that GCN5L1-knockout mice lack HADHA that is hyperacetylated at three specific lysine residues (Lys-350, Lys-383, and Lys-406) and that acetylation at these sites is significantly associated with increased HADHA activity. We conclude that GCN5L1-mediated regulation of mitochondrial protein acetylation plays a role in hepatic metabolic homeostasis.

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

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