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ORIGINAL RESEARCH

Association of Variants of Arginine Vasopressin and Arginine Vasopressin Receptor 1A With Severe Acetaminophen Liver Injury

Matthew Randesi,[1] Orna Levran,[1] Joel Correa da Rosa,[2] Julia Hankins,[3] Jody Rule,[4] Mary Jeanne Kreek,[1,b] and William M. Lee,[4,b] for the Acute Liver Failure Study Group

[1]Laboratory of the Biology of Addictive Diseases and [2]Center for Clinical and Translational Science, Rockefeller University, New York, New York; and [3]Center for the Genetics of Host Defense and [4]Division of Digestive and Liver Diseases, Department of Internal Medicine, UT Southwestern Medical Center at Dallas, Dallas, Texas

SUMMARY

Acetaminophen (APAP)-related acute liver injury/liver failure (ALF) often appears to occur in the setting of substance abuse. We identified two single nucleotide polymorphisms previously associated with drug use disorder in a carefully adjudicated group of APAP ALF patients.

BACKGROUND & AIMS: Acetaminophen-related acute liver injury and liver failure (ALF) result from ingestion of supratherapeutic quantities of this analgesic, frequently in association with other forms of substance abuse including alcohol, opioids, and cocaine. Thus, overdosing represents a unique high-risk behavior associated with other forms of drug use disorder.

METHODS: We examined a series of 21 single nucleotide polymorphisms (SNPs) in 9 genes related to impulsivity and/or stress responsivity that may modify response to stress. Study subjects were 229 white patients admitted to tertiary care liver centers for ALF that was determined to be due to acetaminophen toxicity after careful review of historical and biochemical data. Identification of relevant SNPs used Sanger sequencing, TaqMan, or custom microarray. Association tests were carried out to compare genotype frequencies between patients and healthy white controls.

RESULTS: The mean age was 37 years, and 75.6% were female, with similar numbers classified as intentional overdose or unintentional (without suicidal intent, occurring for a period of several days, usually due to pain). There was concomitant alcohol abuse in 30%, opioid use in 33.6%, and use of other drugs of abuse in 30.6%. The genotype frequencies of 2 SNPs were found to be significantly different between the cases and controls, specifically SNP rs2282018 in the arginine vasopressin gene (*AVP*, odds ratio 1.64) and SNP rs11174811 in the AVP receptor 1A gene (*AVPR1A*, odds ratio 1.89), both of which have been previously linked to a drug use disorder diagnosis.

CONCLUSIONS: Patients who develop acetaminophen-related ALF have increased frequency of gene variants that may cause altered stress responsivity, which has been shown to be associated with other unrelated substance use disorders. *(Cell Mol Gastroenterol Hepatol 2017;3:500–505; http://dx.doi.org/10.1016/j.jcmgh.2017.01.008)*

Keywords: Impulsivity; Stress Responsivity; Pituitary-Adrenal Axis; Overdose.

Acetaminophen (APAP)-induced liver injury is the most common cause of acute liver failure (ALF) in American adults,[1] with nearly 500 deaths annually attributed to excessive dosing of this ubiquitous pain reliever. The safe upper limit for daily dosing has variably been thought to be 4000 mg/day or possibly less.[2] Excessive APAP dosing can occur with intent of self-harm (suicide attempt) or unintentionally while seeking pain relief, typically for a period of several days by using increased amounts each day.[3,4] Early on, an association was made between alcohol abuse and APAP unintentional overdoses, referred to initially as therapeutic misadventure.[5] Both intentional and unintentional APAP overdoses have been shown to be associated with substance abuse of both alcohol and opioids, particularly the opioid (hydrocodone/acetaminophen) combination products.[6] In 1 study of 275 APAP-related ALF patients, 55% had a history of alcohol use and 35% a history of alcohol abuse, and 53% had taken an opioid-APAP combination product.[4] In a follow-up study of a larger cohort of 306 APAP toxicity survivors, 55% had a history of psychiatric disease compared with only 27% of non-APAP survivors, 46% of APAP patients had a history of prior substance abuse vs 15% of non-APAP patients, and 14% had a specific history of injection drug use vs 8% for the non-APAP group.[7] Understanding what determines these behaviors might lead to better identification of high-risk patients and development of prevention strategies.

With either intentional or unintentional etiologies, critical behavioral differences could lead to high-risk behaviors.

[b]Authors share co-senior authorship.

Abbreviations used in this paper: **ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; APAP, acetaminophen; SNP, single nucleotide polymorphism.**

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Impulsivity is a character trait defined as "acting suddenly in an unplanned manner to satisfy a desire," ie, not thinking things through to understand the potential impact of a decision. More recently, impulsivity has been recognized as a measurable trait that is correlated with a variety of addictive behaviors.[8] We have recently shown that higher impulsivity scores on the Barratt impulsivity scale are detected in both intentional and unintentional APAP overdoses when compared with control populations (Sanders C, Lee WM, unpublished data, submitted for publication).

During the last 15 years numerous single nucleotide polymorphisms (SNPs) have been found to be associated with addictive behavior, including impulsivity.[8–10] Many of these SNPs are in genes associated with the stress response, including the genes involved in hormonal systems of the hypothalamic/pituitary/adrenal axis.[11–18] For example, the μ-opioid receptor gene, *OPRM1*, has polymorphisms, specifically A118G, that have been linked to increased vulnerability/susceptibility to alcohol and opioid addiction.[11,14,15,19] The μ-opioid receptor is used by both exogenous and endogenous opiates and can exert control over stress responsivity, addiction, and withdrawal. We hypothesized that this polymorphism or others that are related may have an impact in patients with APAP overdoses, especially in patients who have multiple substance dependencies. Furthermore, we speculated that the genetic association may be stronger or more apparent in subjects with intentional APAP overdose compared with those with nonintentional overdose. Thus, variations in several of these genes that alter the host's ability to respond to stressful situations may indeed correlate with the observed tendency of addictive behavior.

The Acute Liver Failure Study Group (ALFSG) (ClinicalTrials.gov: NCT00518440) has been prospectively identifying and studying the etiologies, presenting features, and clinical outcomes of adults with ALF during the past 17 years while collecting biosamples—serum, plasma, and DNA. During this time period, ALFSG has enrolled more than 3000 subjects in its registry, 46% of whom suffered from severe or fatal APAP liver injury. Because stress and the response to stress are closely linked to addictive behavior and APAP toxicity patients have frequently been identified as substance abusers, we sought to determine whether specific variants in stress-related genes are over-represented in an APAP overdose cohort compared with population controls. By using DNA from 229 of these APAP subjects, we sought to identify whether selective variants in genes related to stress/impulsivity and addiction are associated with APAP overdose cases, because these findings might shed light on the patients' tendency to abuse APAP products.

Methods

Patients

Among the 1669 subjects who were enrolled in the ALFSG registry database between January 1, 2002 and December 31, 2013 according to principles established in the initial ALFSG report,[1] we selected a consecutive group of patients with unequivocal APAP in whom DNA had also been collected as part of enrollment. Subjects in the overall adult ALFSG registry were enrolled from 33 academic centers in the United States and met criteria for ALF, namely coagulopathy (international normalized ratio $\geq$ 1.5) and grade 1–4 of hepatic encephalopathy, within 26 weeks of the first symptoms, without overt underlying liver disease. Because patients enrolled are by definition encephalopathic, written informed consent was obtained from the legal next of kin in each case. Demographic, clinical, laboratory, radiologic, and outcomes data were recorded prospectively. For the purpose of the present study, we selected only patients who self-reported as white.

Etiologic diagnoses were made by each study site's primary investigator on the basis of the history and clinical presentation and laboratory, radiographic, and, when available, liver biopsy results. Further adjudication was provided by using an algorithm for confirmation of APAP overdoses developed by the ALFSG causality subcommittee. The algorithm includes the following specific criteria: a history of APAP ingestion, detection of APAP in plasma, biochemical pattern that is consistent with APAP toxicity with high serum aminotransferase levels ($\geq$1000 IU/L) along with total bilirubin $<$10.0 mg/dL at presentation, and, if available, presence of APAP-Cys adducts. These criteria have been validated previously in the ALFSG cohort.[4] All subjects were considered to fit the patient phenotype as highly likely/definite APAP toxicity if they met the criteria for history of ingestion and/or parent compound detectable, with appropriate biochemistries as outlined.

Intentionality (intentional/suicidal/single time point vs unintentional [typically for pain relief, suicide denied]) was determined by the site investigator on the basis of findings outlined in Schiødt et al.[3] The control subjects (n = 208) were healthy volunteers ascertained by the Laboratory of the Biology of Addictive Diseases at the Rockefeller University who were previously genotyped on a custom Illumina addiction array for other studies.[13,17]

Genotyping

Genes/single nucleotide polymorphism selection. Nine genes were selected on the basis of their known involvement with impulsivity and/or stress responsivity. A total of 21 SNPs from these 9 genes were selected on the basis of previous reports of potential functionality and/or association with impulsivity and stress responsivity (Table 1). These SNPs were chosen because they were previously found to be associated with heroin and/or cocaine dependence or show changes in their gene expression when exposed to the drug. The μ-opioid receptor (*OPRM1)* variants, rs1799971 (A118G) and rs1799972 (C17T), have previously been linked to both alcohol and heroin addiction.[14,15,19,20] We have previously shown the catechol-O-methyltransferase (*COMT*) variants, rs4680 and rs4818, to be associated with opioid dependence.[21] The variants in FK506 binding protein 5 (*FKBP5*), galanin (*GAL*), arginine vasopressin (*AVP*), arginine vasopressin receptor 1A (*AVPR1A*), corticotropin releasing factor (*CRH*), and CRH receptors 1 and 2 (*CRHR1* and *CRHR2*) were chosen for study because they have been found to be associated with a greater vulnerability for dependence, or