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Is family history of alcohol dependence a risk factor for disturbed sleep in alcohol dependent subjects?

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ABSTRACT

Background: Disturbed sleep and a family history of alcohol dependence (AD) are risk factors for developing AD, yet the underlying relationship between them is unclear among individuals with AD. Understanding these inherited associations will help us not only identify risk for development of these comorbid disorders, but also individualize treatment at this interface. We evaluated whether a first-degree family history of AD (FH+) was a risk factor for sleep continuity disturbance in patients with AD. We also evaluated whether alcohol use or mood disturbance moderated the relationship between FH and sleep.

Methods: We analyzed cross-sectional baseline data from an alcohol clinical trial in a sample of individuals with AD (N = 280). Their family history of AD among nuclear family members, sleep complaints, alcohol use (over the last 90 days), and mood disturbance were assessed using the Family History Interview for Substance and Mood Disorders, Medical Outcomes Study Sleep Scale, Time Line Follow-Back Interview, and Profile of Mood States–Short Form, respectively.

Results: A FH + status (65% of subjects) was significantly associated with lower model estimated mean sleep adequacy (β = - 7.05, p = 0.02) and sleep duration (β = - 0.38, p = 0.04) scale scores. FH was not associated with sleep disturbance scale. No significant moderating effect involving alcohol use or mood disturbance was seen.

Conclusion: Family history of AD is a unique risk factor for sleep complaints in AD. Non-restorative sleep and sleep duration may be noteworthy phenotypes to help probe for underlying genotypic polymorphisms in these comorbid disorders.

1. Introduction

Disturbed sleep continuity is a common complaint in individuals with alcohol dependence (AD) (Chakravorty et al., 2016). These sleep-related problems in alcohol-dependent individuals may include difficulty falling asleep, difficulty staying asleep, unsatisfactory quality of sleep, and/or abnormalities of sleep duration (John et al., 2005; Schuckit and Bernstein, 1981); see Table 1 for details on terminologies. Because sleep continuity disturbance is common in AD and is associated with negative health outcomes, such as suicidal ideation and relapse to drinking (Chakravorty et al., 2016), it is important to identify the underlying etiologic mechanisms of these comorbid disorders. Understanding these etiologic mechanisms will help us identify people at risk of developing comorbid AD and sleep-related problems and develop individualized treatments at this interface.

A preliminary step towards this goal is to assess family history of AD (FH) as a correlate of sleep-related complaints. FH may represent an underlying heritable neurobiological unit of disease. Alternatively, it may represent susceptible genetic material that produces sleep problems when activated by environmental factors, e.g., alcohol use and stress. Such an association between a family history of AD and disturbed sleep will advance knowledge at this interface in two ways. First, we will be able to comprehend whether FH is linked with a specific sleep phenotype. Second, if such a "proof-of-concept" is repeated in other studies, this relationship may be the starting point for comprehending their underlying mechanisms.

Evidence for the association between FH and sleep problems comes from four areas of prior research— heritability estimates, candidate

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Table 1
Glossary of terminologies used in this manuscript.

Domain	Terminology	Explanation
Alcohol	Alcohol Dependence (AD)	A condition of physical or psychological dependence on alcohol leading to problems (DSM-IV diagnosis)
	DD	Drinking Days (frequency); the total number of drinking days over the assessment period (90 days for this study)
	DrPDD	Drinks per drinking day (quantity); the total number of drinks consumed/total drinking days over the last 90 days
Inheritance	Heritability (h^2)	The proportion of variation for a given trait in a population that is due to genetic variation (range 0 – 1)
	Family History (FH)	A record of alcohol dependence in the individual's immediate relatives (father, mother and siblings)
	Positive Family History (FH+)	The presence of family history of alcohol dependence in the individuals immediate relative (first-degree relatives)
	Negative Family History (FH-)	The absence of family history of alcohol dependence in the individuals immediate relative (first-degree relatives)
Sleep	Difficulty falling asleep	Requiring more than 30 minutes to fall asleep after lying down in bed
	Difficulty staying asleep	Interruption of sleep continuity with awakening/s, after falling asleep, with/without difficulty falling back sleep
	Sleep quality	A measure of tiredness when awakening from sleep and feeling rested and restored (PMID: 18363315)
	Alpha band	Electroencephalographic waveforms in the 8-14 Hertz range and seen during relaxed a state
	Beta band	Electroencephalographic waveforms in the 16-31 Hertz range and seen during aroused or anxious state
	Gamma band	Electroencephalographic waveforms > 32 Hertz and seen during active sensory and cognitive processing tasks
	Sleep disturbance scale	A scale assessing difficulty falling asleep (quantity and frequency) and frequency of staying asleep in past 4 weeks
	Sleep adequacy scale	A scale assessing frequency of non-restful sleep and frequency of getting the needed amount of sleep in past 4 weeks
	Sleep duration scale	The number of hours an individual slept at night on a habitual basis over the past 4 weeks

gene studies, electro-physiologic studies, and clinical assessments. Prior research has demonstrated that both AD and sleep disturbance are disorders with a unique familial component. Heritability estimates for AD range from 50% to 60% (Ducci and Goldman, 2008; Grant, 2000; Kendler et al., 1994; Prescott et al., 2005; Prescott et al., 2004), whereas those for sleep disturbance range from 17% to 71% (Gehrman et al., 2013). In prior genetic studies, variations of PER2 and PER3 circadian clock genes have been linked with greater alcohol consumption and sleep disturbance (Brower et al., 2012; Comasco et al., 2010; Kovanen et al., 2010).

Electroencephalographic studies have shown a link between FH and sleep-wake rhythms. Dahl and colleagues demonstrated the interaction between family history and gender on power in the alpha band during sleep. Boys with a family history of AD (FH+) had increased spectral power in the alpha band during sleep when compared to boys without a FH of AD (FH-). No such difference was observed between FH + and FH- girls (Dahl et al., 2003). Tarokh and colleagues revealed an association between FH and the delta band during NREM sleep. FH + teenagers had lower normalized power in the delta band of sleep when compared to FH- subjects (Tarokh and Carskadon, 2010). Increased activity in the slow frequency alpha and beta range in waking electroencephalograms (EEGs) has also been demonstrated in FH + individuals (Porjesz et al., 2005). Coincidentally, Perlis and colleagues have reported such high-frequency EEG activity in patients with insomnia (Perlis et al., 2001a; Perlis et al., 2001b).

From a clinical perspective, FH + individuals have a higher lifetime prevalence of AD (Grant, 1998) and a lower subjective sleep duration compared to FH- individuals (Conroy et al., 2015; Schuckit and Bernstein, 1981). The FH + subtype of AD has been characterized by an early onset of drinking, comorbid psychiatric disorders, and an increased likelihood to seek help for their drinking (Moss et al., 2007; 2010).

In brief, FH may confer a risk for sleep problems in AD, and these problems may be magnified by alcohol consumption and mood disturbance, known correlates of sleep-related complaints (Brower et al., 2001; Chakravorty et al., 2013; Zhabenko et al., 2012). In this hypothesis-generating study, we evaluated the relationship of FH with several sleep-related complaints in a sample of actively drinking subjects with AD. We postulated that subjects with FH + status as compared to FH- status would have higher sleep disturbance and lower perceived sleep adequacy and sleep duration scale scores. In turn, an interplay between FH + status and alcohol use or mood disturbance would lead to more disturbed sleep.

2. Materials and methods

2.1. Design

Cross-sectional data were collected from treatment-seeking alcohol-dependent subjects during a pretreatment evaluation for an interventional study at the Perelman School of Medicine conducted between 2003 and 2008, which was a placebo-controlled trial of naltrexone paired with a behavioral intervention for the cessation of drinking; clinicaltrials.gov identifier NCT00115037 (Lei et al., 2012).

2.2. Participants

Study Subjects (n = 280) were 18 years of age or older, met past year criteria for a DSM-IV diagnosis of AD, consumed alcohol regularly in the 90 days prior to assessment, and were not in acute alcohol withdrawal. Subjects were excluded if they met past year criteria for dependence on drugs (except for cannabis or nicotine), had significant psychiatric or medical illness, used any psychotropic medication on a regular basis, or were currently pregnant, as described previously (Lei et al., 2012). The Institutional Review Board at the Perelman School of Medicine of the University of Pennsylvania approved the study, and each participant gave written, informed consent before enrollment in the study.

2.3. Assessments

2.3.1. Structured clinical interview for DSM-IV (SCID; First et al., 2002)

The SCID instrument, a structured interview, was used to assess criteria for AD in the past year.

2.3.2. Min. International neuropsychiatric interview (MINI; Sheehan et al., 1998)

The MINI version 5.0.0 modules were used to assess other psychiatric diagnoses, including bipolar disorder, panic disorder, post-traumatic stress disorder, generalized anxiety disorder, psychotic disorder, and current dependence on other drugs.

2.3.3. Addiction severity index (ASI; McLellan et al., 1980)

The ASI was used to obtain baseline demographic data and to evaluate between-group differences (FH + vs. FH-) on AD variables including the age of onset of AD and the number of years of lifetime alcohol use. Participants also rated their distress from alcohol use (in the past 30 days) and the importance to them of receiving treatment for AD on a 5-point Likert scale, response options for which included the following: "not at all," "slightly," "moderately," "considerably" and "extremely."

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