Cytokine polymorphisms are associated with daytime napping in adults living with HIV

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Objective/background: Daytime napping longer than one hour has been associated with an increased risk for all-cause mortality. Associations between cytokine polymorphisms and daytime napping in chronic illnesses such as HIV, however, have not been well described. The purpose of this study was to examine cytokine polymorphisms associated with long daytime napping in adults living with HIV.

Methods: A cross-sectional analysis was conducted using a convenience sample of 257 adults living with HIV. Daytime napping was assessed with wrist actigraphy data collected over three days. Participants categorized as long nappers (≥60 min) were compared to short nappers and non-nappers (<60 min).

Results: After adjusting for relevant demographic and clinical characteristics, long daytime napping was associated with 12 SNPs from seven genes: 1) IFNG rs2069728; 2) IL1B rs1143642, rs1143627, and rs16944; 3) IL2 rs2069763; 4) IL6 rs4719714, rs1554606, and rs2069845; 5) IL17A rs3819024 and rs8193036; 6) NFKB1 rs4648110; and 7) NFKB2 rs1056890.

Conclusions: Cytokine genetic variations may have a role in physiological regulation of daytime napping as well as nocturnal sleep. Cytokine polymorphisms associated with long daytime napping could help identify adults with HIV who may benefit from targeted therapeutic interventions.

1. Introduction

Recent meta-analysis studies have suggested that daytime napping is an indicator of increased all-cause mortality [1,2]. Although some beneficial effects of a short nap have been suggested [3], daytime napping of one hour per day or longer has been associated with an increased risk of cardiovascular disease [1] and all-cause mortality [1,4]. Laboratory studies in healthy adults have shown that a short nap after experimental sleep deprivation can restore cognitive impairment and immune function [5–7]. However, long daytime naps that contain delta stage 3–4 non-rapid eye movement (NREM) can lead to impaired alertness after awakening [5,8]. Even in healthy young adults, daytime napping has been associated with daytime sleepiness, depression, and problems with daytime functioning [9].

Adults living with human immunodeficiency virus (HIV) frequently report sleep problems [10], and up to 55% of adults living with HIV experience daytime sleepiness or drowsiness [11,12]. In chronic illnesses like HIV, daytime sleepiness has been associated with poor medication adherence and cognitive...
impairment [13,14]. Due to successful therapies for their HIV infection, these patients are living longer with multiple comorbidities [15]. Taking a long daytime nap may influence daily function or adherence to antiretroviral therapy and other complex medical regimens related to comorbidities. Studies in the HIV population have focused on nocturnal sleep duration, sleep maintenance or sleep quality, and daytime sleepiness [12,16,17]. Daytime sleep behavior has not been well studied in this chronic illness population and underlying mechanisms are unclear. One potential mechanism linked to daytime napping in HIV may involve the inflammatory process.

The HIV virus settles in perivascular macrophages and microglial cells in the brain, inducing an immune response that produces viral and inflammatory proteins [16,18] and secretes cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα), and interferon-gamma (IFNγ) [19]. These cytokines are involved in induction of NREM sleep, and may change diurnal sleep–wake patterns by promoting long daytime napping [20,21]. Inflammation and cytokine activity play an important role in sleep disturbance in chronic illness [22,23]. Nuclear factor of kappa light polypeptide gene enhancer in B cells (NFκB) and cytokines, such as IL-1β, IL-6, and TNFα are known to be involved in sleep regulation [22,23]. We previously reported that polymorphisms of IL1R2, IL2, and TNFA were associated with nocturnal sleep maintenance [17] and polymorphisms of IL1B, IL6, IL13, NFKB1, and TNFA were associated with sleep-onset insomnia in this sample of HIV-infected adults [24]. Elevated plasma levels of TNFα and IL-6 in individuals with sleep apnea, and elevated TNFα plasma levels in individuals with narcolepsy, have been reported if these individuals also experienced excessive daytime sleepiness [25].

Given these prior findings and the need to better understand the mechanisms underlying daytime napping behavior in chronic illness, the purpose of this study was to examine associations between cytokine-associated polymorphisms and daytime napping in adults living with HIV. Based on the findings of prior studies [1,4], this initial association study focused on long daytime napping, defined as daytime sleep of 60 min or longer as objectively estimated by wrist actigraphy.

2. Methods

The Symptom and Genetic Study is a longitudinal study with a convenience sample of adults living with HIV/AIDS aimed at identifying biomarkers of symptom experience among HIV-infected adults [10]. This cross-sectional analysis focuses on potential cytokine-related genetic markers of daytime napping. The study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF). Study participants were recruited using flyers at HIV clinics and community sites in the San Francisco Bay Area. All participants provided written informed consent and signed a Health Insurance Portability and Accountability Act release to access their protected medical information for this research.

Participants were included if they were English-speaking adults at least 18 years of age who had been diagnosed with HIV at least 30 days before enrollment. To specifically address HIV-related symptom experience, potential participants were excluded if they currently used illicit drugs (as determined by self-report or by positive urine drug testing), worked nights (ie, at least four hours between 12:00 AM and 6:00 AM), reported having bipolar disorder, schizophrenia, or dementia, or were pregnant within the prior three months. Participants with insomnia were not excluded, but those with other diagnosed sleep disorders, such as apnea and narcolepsy were excluded.

2.1. Sample characteristics

Demographic characteristics of age, gender, race/ethnicity, education, employment, and income were collected using a demographic questionnaire. Years since HIV diagnosis and current medication regimen were obtained through self-report. The most recent CD4+ T-cell count and HIV viral load values, and hemoglobin values to determine anemia were obtained from patients’ medical records. While most lab values were obtained within 45 days of the study visit, values up to six months old were included in the analysis. Medications were categorized as antiretroviral therapy (ART), sleep, anti-depressant, or opiate, based on the potential for such medications to impact daytime napping. Trained research staff obtained blood pressures and measures of weight in kilograms and height in meters to calculate body mass index (BMI; weight divided by squared height) during a Clinical Research Center clinic appointment visit; these measures were evaluated as potential covariates because of their associations with daytime napping and cardiovascular disease.

2.2. Biomarkers

2.2.1. Fasting blood samples

Fasting blood samples were obtained from each participant during a morning Clinical Research Center visit. These samples were then delivered to the laboratory for short term storage at 4 °C until processed. Processing typically occurred within 24 h. Samples were processed for their plasma by ultracentrifugation and isolation of genomics DNA. Processed samples were then stored at −80 °C. Plasma levels of six cytokine analytes associated with sleep regulation (ie, IL-1β, IL-2, IL-6, IL-10, IL-13, TNFα) were assayed using the Luminex xMAP multiplex platform (BioMarker Services, EMD Millipore, St. Charles, MO). IL-4 was also included in the assay panel, but most values were below the lower limit of detection; thus IL-4 was excluded from analyses.

2.2.2. Gene selection and genotyping

Fifteen cytokine candidate genes involved in cytokine signaling were selected for analysis based on their known influence on inflammatory processes: interferon-gamma (IFNγ), IFNγ receptor 1 (IFNGR1), interleukins (IL1B, IL1R1, IL1R2, IL2, IL4, IL6, IL8, IL10, IL13, IL17A), NFKB1, NFKB2, and TNFA. Genomic DNA was extracted from peripheral blood mononuclear cells and maintained by the UCSF Genomic Markers of Symptoms Tissue Bank [26,27] using the PUREGene DNA Isolation System (Invitrogen, Carlsbad, CA). Of the 350 participants recruited, DNA could be isolated from 348.

Genotyping was performed blinded to clinical status and included positive and negative controls. DNA samples were quantitated with a Nanodrop Spectrophotometer (ND-1000) and normalized to a concentration of 50 ng/μL (diluted in 10 mM Tris/1 mM EDTA). Samples were genotyped using the GoldenGate genotyping platform (Illumina, San Diego, CA) and processed according to the standard protocol using GenomeStudio (Illumina, San Diego, CA). Signal intensity profiles and resulting genotype calls for each single nucleotide polymorphism (SNP) were visually inspected by two blinded reviewers. Disagreements were resolved by a third reviewer.

2.2.3. Selection of single nucleotide polymorphisms (SNPs)

A broad panel of SNPs involved in cytokine signaling was selected for this initial study based on their known influence on inflammatory processes. The panel included a combination of tagging SNPs and literature driven SNPs (ie, SNPs reported as being associated with altered function) [17,24,26–29]. Tagging SNPs were required to be common (defined as having a minor allele frequency...
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