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Short communication

Infection with Herpes Simplex virus type 1 (HSV-1) and sleep: The dog that did not bark

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ABSTRACT

Persistent infection with Herpes Simplex viruses (HSV) and other brain infections is consistently associated with cognitive impairment. These infections can also affect sleep. Thus, sleep abnormalities could explain the cognitive dysfunction. We investigated the association between sleep variables and persistent HSV-1, HSV-2, cytomegalovirus (CMV) and *Toxoplasma gondii* (Tox) infections. Sleep data were collected from older adults with or without insomnia (N = 311, total); a subset completed polysomnographic and actigraphy studies (N = 145). No significant associations were found between the infections and insomnia or the remaining sleep variables following corrections for multiple comparisons. Sleep dysfunction is unlikely to explain the infection-related cognitive dysfunction.

1. Introduction

Human infection with Herpes Simplex virus, type 1 (HSV-1) is a major public health problem. In 2015–2016, 47.8% of persons aged 14–49 in the United States were infected with HSV-1 (McQuillan et al., 2018). Primary infection with HSV-1 is usually asymptomatic, though it causes severe encephalitis rarely (Kawada, 2018). Typically, primary infection progresses to latent infection, during which the virions are harbored in neurons in a relatively inactive state. Reactivation leads to lytic infection in mucosal surfaces and in the cornea (Thellman and Triezenberg, 2017). Though persistent or latent infection are considered benign, numerous reports indicate that persistent infection is associated with cognitive impairment even without encephalitis (Aiello et al., 2006; Fruchter et al., 2015; Jonker et al., 2014; Katan et al., 2013; Nimgaonkar et al., 2016; Strandberg et al., 2003; Tarter et al., 2014; Thomas et al., 2013; Watson et al., 2013; Wright et al., 2015). The cognitive impairment has been noted particularly among patients with schizophrenia or bipolar disorder (Dickerson et al., 2012, 2004, 2003; Gerber et al., 2012; Hamdani et al., 2017; Prasad et al., 2011, 2012; Schretlen et al., 2010). It can be progressive and may be amenable to antiviral treatment (Bhatia et al., 2018; Prasad et al., 2013). The mechanism of the cognitive dysfunction is unknown.

Sleep dysfunction is a plausible mechanism for the HSV-1 associated cognitive dysfunction. Many infections are associated with sleep disruption. For example, infection with the Human Immunodeficiency Virus (HIV) is associated with cognitive dysfunction (Clifford and Ances, 2013) and abnormalities in sleep such as more frequent awakenings after sleep onset, decrease of REM sleep, sleep spindles and K-complexes (Kubicki et al., 1989; Norman et al., 1992). The sleep disturbances can become more severe as the infection progresses alongside the cognitive changes (Kubicki et al., 1989).

In the present investigation, we assessed the association between sleep abnormalities and persistent HSV-1 infection due to extensive reports in the research literature indicating an association between persistent HSV-1 infection and cognitive impairment (Fruchter et al., 2015; Jonker et al., 2014; Nimgaonkar et al., 2016; Tarter et al., 2014; Tucker and Bertke, 2019; Wright et al., 2015). For comparison, we also investigated infections with Herpes Simplex, type 2 (HSV-2, Cytomegalovirus (CMV) and *Toxoplasma gondii*(Tox). These agents also cause prevalent, lifelong infection, can infect the brain, and are associated with cognitive impairment (Dickerson et al., 2014; Hamdani et al., 2017).

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2. Methods

2.1. Study site

Participants were recruited at the Western Psychiatric Institute and Clinic (WPIC), Pittsburgh, Pennsylvania.

2.2. Study design

The study included older adults with insomnia (OAI) and normal/'good' sleepers (GS).

2.3. Participants

Participants were drawn from a larger prior study entitled "Aging Well, Sleeping Efficiently: Intervention Studies" (AgeWise) program project (AG020677) (Hall et al., 2008; Wilckens et al., 2016; Mansour et al., 2017). Initially, 323 participants were screened, 311 participated in our analysis. The study had two phases. In the first phase, all participants completed pen and paper evaluations of sleep patterns; they were also evaluated for additional inclusion/exclusion criteria for the AgeWise program (Hall et al., 2008). In the second phase, participants who fulfilled the additional inclusion/exclusion criteria completed detailed sleep evaluations, including polysomnography and actigraphy.

The sample included OAI or GS. OAI fulfilled both ICSD-2 criteria for general insomnia disorder and DSM-IV criteria for primary insomnia, as indicated by the following: A complaint of poor sleep; adequate opportunity for sleep; a complaint of daytime impairment; and duration of at least one month. Severity criteria included an Insomnia Severity Index (ISI) score ≥ 14; mean diary-based sleep latency or wake after sleep onset value of ≥ 31 min; and mean diary-based sleep efficiency (SE) $\leq 85\%$ on screening sleep diary. Good sleepers (GS) did not meet ICSD-2, DSM-IV, or sleep diary criteria for insomnia disorder, and had ISI scores <7. All AgeWise II participants were ≥ 60 years old. Participants in both groups had stable medical conditions, were not currently taking sleep medications, and consumed ≤ 3 caffeinated beverages per day and ≤ 7 alcohol beverages per week.

2.4. Sleep variables obtained from all participants (N = 311)

The following self-reported questionnaires were answered by all participants initially ($N = 311$): the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) to describe self-reported sleep quality; the Physical Health and Mental Health Component Summary measures of the Medical Outcomes Survey Short Form 36 (SF-36) (Ware and Sherbourne, 1992) to describe mental and physical health-related quality of life; the Smith morningess–eveningness composite scale and the Epworth sleepiness scale (ESS) to assess the tendency to doze in 8 specific circumstances (Johns, 1991). Participants also completed a daily sleep diary for 2 weeks (Monk et al., 1994). All the variables were considered as outcomes of interest; they were continuous and are listed in Supplementary Table 1.

The second phase of the study was completed by a subset of the participants ($n = 145$) who underwent polysomnography (PSG) and actigraphy protocols.

2.5. Polysomnography (from selected OAI and GS participants, N = 145)

The PSG montage included bilateral central referential EEG channels (C3 and C4, referenced to A1–A2), electro-oculogram (EOG), (EMG) and electrocardiogram (EKG). EEG power in the 0.5–4 Hz band was calculated for each minute of NREM sleep, averaged for all minutes of NREM sleep, and divided by the average total power from 0.5 to 32 Hz during all minutes of NREM sleep (Supplementary Table 1).

2.6. Estimating viral exposure

Detecting HSV-1 in body fluids is difficult. It is more reliable to index infectious exposure through highly specific and sensitive antibodies in the serum or plasma (Watson et al., 2009). Serum was extracted from peripheral venous blood samples and stored at $-80\,^{\circ}C$ for serological analysis. Serum levels of Immunoglobulin G (IgG) antibody to CMV, HSV-1, HSV-2 and Tox were estimated using microplate solid-phase enzyme immunoassays (ELISA) (Dickerson et al., 2003). Using standardized cutoff values, individuals were classified as seropositive or seronegative. We also analyzed the data using antibody titers as quantitative (continuous) variables.

2.7. Statistical analysis

Analyses of primary sleep-related outcomes were conducted using generalized linear models, with binary pathogen exposure as the primary predictor (serostatus, 'present/absent'), controlling for sex, age and race. Sensitivity analyses additionally included patient type (OAI or GS) to determine whether any results were influenced by the fact that the participant pool was made up of two distinct groups with significantly different sleep. Our primary pathogen of interest was HSV-1. Separate analyses were conducted using exposure data for HSV-2, CMV, and Tox as primary predictors. The additive effect of exposure across all four pathogens was also considered by summing binary exposure/non-exposure across the four pathogens. For those with no positive exposure this variable is 0, for those with exposure to one pathogen it is 1, for those with exposure to two pathogens it is 2 and so forth. A third tier of analysis was conducted by covarying for insomnia status, including interactions between exposure and insomnia status. We also examined the continuous measures of exposure, i.e., IgG antibody titers. Analysis of demographic and exposure variables between OAI and GS was conducted using the Fisher's exact test or the Student's *t*-test as appropriate.

We evaluated study-wide significance after FDR adjustment for multiple comparisons; however, we have also stated nominal statistical significance ($p = 0.05$). All analyses were conducted using the Statistical Package for Social Sciences (SPSS v22).

3. Results

3.1. Demographic variables

The overall sample of older adults included 131 normal sleeping participants and 180 participants suffering from insomnia. The majority of participants reported Caucasian ethnicity (89%). There were no significant differences between the normal sleepers and insomnia cases with respect to age, gender or race (Table 1). There were no significant differences between Caucasians and other ethnic groups with regard to prevalence of HSV-1, CMV, and Toxo serostatus, however the prevalence of HSV-2 was higher among African-Americans, as reported (Gottlieb et al., 2002). There were no significant differences in ethnicity or HSV-1 exposure between OAI and GS.

3.2. Associations between HSV-1 serostatus and insomnia

We studied the relationship between HSV-1 serostatus and sleep variables in two ways. First, we compared normal sleepers and persons with insomnia with regard to serostatus. Generalized linear models were employed for analysis of IgG antibody titers (continuous variables), binary logistic models were employed for binary exposure serostatus and all models included sex, age and reported race as covariates. No significant differences were detected between these two groups with regard to serostatus for any of the infectious agents or for antibody titers (Table 1). Next, we considered the sleep variables as outcomes and related them to serostatus as predictor variables.

Table 1
Group demographics and Levels of antibodies to infectious agents.

Group	Demographics			Herpes Simplex, type 1 (HSV-1)		Herpes Simplex, type 2 (HSV-2)	Cytomegalovirus (CMV)		*Toxoplasma gondii*(Tox)	
	Sex (male/female)	Age in years (mean ± SD[a])	Race (Caucasian/African-American/Asian)	Sero-status[b]	Ab titers (mean, S.D.)	Sero-status	Ab titers (mean, S.D.)	Sero-status	Ab titers (mean, S.D.)	Sero-status	Ab titers
Normal sleepers (n = 131)	55/76 (58%/42%)	68.6 ± 7.01	117/13/1 (89%/9.9%/0.8%)	83/48 (63.4/36.6%)	2.0 ± 1.3	40/91 (30.5%/69.5%)	1.0 ± 1.1	90/41 (68.7/31.3%)	3.4 ± 2.2	58/73 (44.3/55.7%)	1.4 ± 1.2
Insomnia (n = 180)	63/117 (65%/35%)	69.4 ± 7.12	159/18/3 (88.3%/10.0%/1.7%)	110/70 (61.1/38.9%)	2.0 ± 1.5	42/138 (23.3/76.7)	0.9 ± 1. 0	123/57 (68.3/31.7%)	3.3 ± 2.2	81/99 (45/55%)	1.6 ± 1.4
Generalized linear model for IgG titers, binary logistic model for binary status				B = 0.14, p = 0.56	B = 0.016, p = 0.92	B = 0.476, p = 0.9	B = 0.188, p = 0.09	B = 0.079, p = 0.76	B = 0.085, p = 0.74	B = 0.019, p = 0.94	B = − 0.153, p = 0.32

[a] S.D.: standard deviation.
[b] Serostatus: number of persons with elevated antibody titers, above a pre-determined threshold. Ab titers: Titers of antibodies to the respective infectious agent IgG.

3.3. Associations between HSV-1 serostatus and sleep variables

We examined 49 variables (34 self-reported sleep variables and 15 polysomnography variables) as outcomes and serostatus as the primary predictor, with age and gender as covariates. HSV-1 seropositive status was associated with only 3 out of 49 variables, at nominal levels of statistical significance (p = 0.05). Similar patterns were obtained when we added insomnia status as a co-variate to examine whether adjusting for binary insomnia status altered the effect of exposure on the outcomes. The outcome variables nominally associated with HSV-1 seropositive status included lower Epworth Sleepiness Scale (ESS) total score, increase variability (standard deviation of Actigraphy total Sleep time across days), and increased NREM stage 2 sleep minutes in polysomnography (Supplementary Table 1). We repeated these analyses using antibody titers for each infective agent as the predictor variables; the results were consistent with the analyses using serostatus as the predictor variable (data not shown). We also sought interactions between exposure and insomnia status. No significant interactions were observed after correcting for multiple comparisons (data not shown).

When the same outcomes were analyzed in relation to HSV-2, CMV and *T. gondii*exposure, 4.1% of variables were associated with seropositive status: 2/49 for HSV-2 (increased Epworth Sleepiness Scale (ESS) total score and reduced *SD* of Diary sleep efficiency), 0/49 for CMV, and 2/49 for Tox (increased Actigraphy mean of sleep latency and increased Actigraphy standard deviation of sleep latency; data not shown). When associations were examined using antibody titers, CMV infection was associated with increased scores on the morningess–eveningness scale. Tox infection was associated with later Actigraphy sleep mid-point and increased *SD* of alertness after awakening.

No significant associations between any pathogenic exposure and any sleep related outcome variable remained significant after correcting for multiple comparisons.

4. Discussion

To our knowledge, this is the first study to examine sleep variables in relation to a set of neurotropic infectious agents that cause lifelong infection. We found no statistically significant evidence of an association between persistent viral infection and either self-reported, actigraphic or polysomnographic sleep measures in older adults, following corrections for multiple comparisons. Similarly, associations with HSV-2, CMV and Tox infections that were nominally significant with a handful of variables did not survive correction for multiple comparisons.

The lack of association between the neurotropic infectious agents and sleep related variables is surprising, because HSV-1 infection is associated with impairment in multiple cognitive domains (e.g., abstraction, flexibility, attention, spatial memory and spatial processing. emotional processing and sensorimotor dexterity) (Thomas et al., 2013). Night sleep is strongly correlated with cognitive function (Kyle et al., 2017; Lo et al., 2016; Mander et al., 2008; Tempesta et al., 2018; Wilckens et al., 2016). Thus, HSV-1 infection would be predicted to cause sleep dysfunction. Further investigation could be instructive, much in the same way that the mythical Sherlock Holmes solved the mystery of a stolen race horse on the basis of a dog that did not bark when the horse was removed from its stable (Doyle, 2011).

It is instructive to compare the patterns of HSV-1 and HIV infection, as the latter is associated with cognitive dysfunction, as well as sleep disruption. HIV and HSV-1 sequester in different parts of the brain; HIV has been identified in the brainstem, thalamus, hippocampus, cerebellum as well as mesial temporal lobe (Zhou et al., 2009) whereas MRI studies show reduced gray matter volume in frontotemporal regions in HSV-1 seropositive persons (Prasad et al., 2012). The nature of neuronal damage caused by HIV and HSV-1 could thus be different and could account for the divergent associations with sleep dysfunction.

Host immunologic responses could also contribute to the sleep

disruption, though the immunologic responses to HIV and HSV-1 differ (Halford et al., 1996; Huang et al., 2016; Shimeld et al., 1999). Cytokines can alter discharge patterns of neurons or interact with neurotransmitters (Opp, 2005) thereby altering sleep architecture in rodents (Pollmacher et al., 2002). In humans, low dose injections of endotoxin increase levels of circulating cytokines and non-rapid eye movement (NREM) sleep and slow wave sleep (SWS, stages 3 and 4) and delta power, whereas higher doses inhibit sleep (Grigoleit et al., 2011). Interferon-gamma therapy for Hepatitis C virus (HCV) infection alters sleep variables (Raison et al., 2010). Granulocyte colony-stimulating factor (G-CSF) also suppresses sleep intensity (Schuld et al., 1999).

Some shortcomings should be noted. The lack of generalizability of the sample in terms of geographic representation and the lack of adjustment for socioeconomic status are acknowledged. The sample size is modest, though cognitive dysfunction has been observed in association with HSV-1 infection in samples of similar size (Shirts et al., 2008; Thomas et al., 2013). We analyzed only older adults. Compared with young adults, elderly people show decreased slow wave sleep and advanced sleep phase, with reduced sleep efficiency and total sleep time (Cooke and Ancoli-Israel, 2011). Sleep changes could be confounded by pathogen exposure as both increase with age.

In conclusion, infection with HSV-1, estimated using antibody titers did not differ between older adults with or without insomnia. Significant associations between HSV-1 infection and sleep disturbances were not detected. Similar patterns were obtained for HSV-2, CMV and Tox. Thus, sleep disturbance might not explain the associated cognitive impairment.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112502.

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