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Increased CD4 counts, pain and depression are correlates of lower sleep quality in treated HIV positive patients with low baseline CD4 counts

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ABSTRACT

Poor sleep quality leads to increased immune activation and immune activation leads to worse sleep quality. South African HIV positive patients typically have delayed start of treatment, which has been associated with CD4+ effector T cells being more spontaneously activated in chronically treated patients. This cross-sectional study investigated whether subjective sleep quality was associated with CD4+ T lymphocyte reconstitution in treated South African HIV+ patients.

One hundred and thirty-nine treated HIV+ patients (109 F, age average (SD) = 43 (9)) were recruited from Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg, South Africa. Participants completed questionnaires evaluating their subjective sleep quality (Pittsburgh Sleep Quality Index), daytime sleepiness (Epworth sleepiness scale), pain, and depression severity (Beck Depression Inventory). Univariate and multivariate analyses were run to determine the correlates of sleep quality in this population.

Patients had been on antiretroviral treatment for about 4 years and had increased their CD4 counts from a median at baseline of 82 to 467 cells/μL. They had overall poor sleep quality (average (SD) PSQI = 7.7 (±5), 61% reporting PSQI > 5, a marker of lower sleep quality), 41% had clinical depression (average (SD) BDI = 17 (±12)) and 55% reported pain. In two separate multivariate analyses, both the overall CD4 count increase from baseline ($p = 0.0006$) and higher current CD4 counts ($p = 0.0007$) were associated with worse sleep quality, when adjusting for depression severity ($p < 0.001$), daytime sleepiness ($p = 0.01$) and the presence of pain ($p < 0.01$).

In this cohort of treated South African HIV positive patients, poor sleep quality was associated with higher current CD4 counts, when adjusting for depression severity, daytime sleepiness and pain. Further studies should investigate the temporal relationship between HIV-related poor sleep quality and underlying immune activation.

1. Introduction

1.1. Sleep and immunity

There is a well-described relationship between sleep and the immune system whereby sleep disturbances have been shown to enhance inflammatory states (Bollinger et al., 2009; Dinges et al., 1999; Irwin et al., 2006; Meier-Ewert et al., 2004; Mullington et al., 2009; Shearer et al., 2001). Conversely inflammatory states also lead to increased sleep disruption (Mullington et al., 2000; Pollmächer et al., 1993). Accordingly, treatment with the pro-inflammatory cytokine IFN alpha has been shown to increase wake after sleep onset, with more spontaneous arousals and to decrease sleep efficiency (Raison et al., 2010). In contrast, treatment with a blocker of the pro-inflammatory cytokine TNF alpha (infliximab) of patients with severe depression and increased CRP levels was shown to decrease wake after sleep onset and improve sleep quality (Weinberger et al., 2015). These findings therefore strongly suggest that immune activation disrupts sleep.

1.2. HIV, sleep, and immunity

1.2.1. In untreated HIV positive patients

Before starting treatment, infection by the retrovirus human immunodeficiency virus (HIV) is associated with chronic activation

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of the immune system (Espindola et al., 2015). Early studies have shown that fatigue and lower sleep quality precede HIV diagnosis and are early symptoms of the infection (Darko et al., 1992, 1995, 1998; Norman et al., 1992, 1990, 1988). In untreated HIV positive patients, the slow wave sleep percentage decreased in the first part of the sleep episode compared to controls, and patients had increased wake after sleep onset (Ferini-Strambi et al., 1995; Norman et al., 1992). HIV-related sleep disturbances have been shown to be associated with the increased immune activation triggered by HIV infection both in rats (Opp et al., 1996) and in humans (Darko et al., 1992, 1995).

1.2.2. In treated HIV positive patients

However, even after starting antiretroviral therapy (ART), HIV positive patients continue reporting lower sleep quality. A 2005 review of 29 studies on HIV and sleep reported that an estimated 40 to 60% of HIV patients (treated or untreated) complain of poor sleep quality (Reid and Dwyer, 2005). A more recent meta-analysis including 27 studies of 9246 HIV positive participants found an overall prevalence of self-reported poor sleep quality of 58% (Wu et al., 2015). A study of 290 American HIV positive patients using actigraphy showed that 45% slept <6 h per night, 34% reported difficulty falling asleep, and 56% had fragmented sleep; with only 30% being good sleepers (Crum-Cianflone et al., 2012). Correlates of poor sleep quality in treated HIV positive patients highlighted by a large body of studies included low CD4 counts (Oshinaike et al., 2014; Seay et al., 2013), depression (Allavena et al., 2016; Barroso et al., 2015; Wibbeler et al., 2012), lower socioeconomic status (Allavena et al., 2016; Crum-Cianflone et al., 2012), the presence of peripheral neuropathy and/or pain (Crum-Cianflone et al., 2012; Vosvick et al., 2004), and treatment by the non nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (Gallego et al., 2004; Nunez et al., 2001; Oshinaike et al., 2014). Recent data show that immune activation may remain a factor in HIV-related lower sleep quality, whereby HIV-related lower sleep quality was shown to be associated with polymorphisms in cytokines including IL1, IL 6 and TNF alpha (Gay et al., 2015).

1.3. HIV in South Africa

To date, populations studied with respect to HIV and sleep have been mainly Caucasian, male and with first world access to care. In contrast, South Africa's HIV positive population, with its staggering prevalence of 12.2% (7 million) of South Africa's total population, is 60% female and 97% of African ancestry (Statistics South Africa, 2016). In addition, due to delayed initial presentation and past treatment initiation guidelines, the majority of HIV positive patients started on ART only when reaching a CD4 count below 200/μL. This delayed start of ART has been associated with higher spontaneous immune activation once CD4 counts have reconstituted (Okulicz et al., 2015). Taken together, these factors differentiate the South African treated HIV positive population in which, as far as we are aware, no study has been done on sleep quality.

We therefore undertook a cross-sectional study of treated HIV positive patients from a South African urban community to determine the prevalence and correlates of sleep quality, in particular focusing on the possible association with a CD4-related immune activation.

2. Methods

2.1. Population and study design

In this cross sectional study, 139 HIV positive patients with baseline CD4 count information were enrolled (152 patients recruited) from the Adult HIV Clinic at the Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg. This tertiary hospital serves an urban community of African ancestry. A nursing sister made an announcement inviting patients who were over the age of 18 years to participate in the study, which was advertised as a study of how well people slept. Potential participants went with the investigator into a separate consulting room. Most patients were fluent in English. HIV counselors acted as translators for 3 of them. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M120411). Informed consent to participate in the study was obtained from each participant prior to enrolment. Recruitment took place over 4 months from May to August 2012.

2.2. Questionnaires

2.2.1. Sleep quality

The Pittsburgh Sleep Quality Index (Buysse et al., 1989) was used to assess sleep quality over the past 30 days. It comprises seven components each taking a value from 0 to 3. Therefore, the PSQI Global score ranges from 0 to 21. A global PSQI score $\leq$5 indicates normal sleep quality while a score >5 indicates poor sleep quality. We used the PSQI global score as the main outcome variable for the study.

2.2.2. Daytime sleepiness

The Epworth Sleepiness Scale (ESS) (Johns, 1991) was used to assess levels of daytime sleepiness. This questionnaire uses 8 questions pertaining to the likelihood in the past 30 days of dozing during the day in different types of circumstances (either being passive or active): each question can take any discrete value from 0 (never) to 3 (high chance). Therefore ESS total score ranges from 0 to 24. An ESS total score >10 indicates the presence of excessive daytime sleepiness and suggests an underlying sleep disorder.

2.2.3. Depression

Beck's Depression Inventory (BDI) (Beck et al., 1961) was used to assess the presence of depressive symptoms and their severity in our cohort. It comprises 21 questions assessing the degree of a depressive symptom on a discrete scale from 0 to 3, with 0 indicating absence of the depressive symptom to 3 indicating the most severe presentation of that symptom. Therefore BDI score ranges from 0 to 63. BDI scores >10 indicate depression, scores >17 indicate moderate to severe depression.

2.2.4. Questionnaires' internal consistency and validity testing for a population using English as a second language

Although most participants at the clinic were fluent in English, English was their second language. To ensure the questionnaires (PSQI, ESS, BDI) we used were reliable in this context, we ran a Cronbach's alpha to test for the internal consistency of each questionnaire and we also ran a factor analysis to assess their construct validity in this cohort.

2.2.5. General information questionnaire

Demographic data, including age, sex, employment status and significant comorbidities, past or present, were collected both from the patient and by checking the clinic record.

The presence of pain in the month prior to enrollment into the study and presence of pain on the study day were noted. If they reported pain on these two questions, we asked them to rate their pain on a 10-point Likert scale going from 1 to 10, with 1 showing the anchor 'no pain' and 10 showing the anchor 'worst pain ever felt' and also to color on a body diagram the site(s) of their pain.