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Sleepiness and sleep quality in patients with HIV infection

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ABSTRACT

Objectives: Patients with HIV infection frequently complain of sleep disturbances and daytime sleepiness. Only few data on these problems evaluated by standardized measures is available.
Methods: A sample of 180 consecutive patients with HIV infection referred to the internal and to the neurological HIV clinics at the University of Münster was enrolled in this study. The data were compared to a sample of 120 age- and sex-matched control subjects. We used the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), and the Beck's Depression Inventory (BDI). In addition, the clinical and immunological data of the patients were registered.
Results: All scores of the ESS, the PSQI, and the BDI were significantly increased in the HIV infected patients as compared to the control group. There were no significant correlations between any of the immune parameters and the scores. Only a higher BDI score was correlated with both the ESS score and the PSQI score.
Conclusions: Patients with HIV infection and not using evavirenz show an increased daytime sleepiness and a decreased quality of sleep. These findings could not be related to the immunological state of the patients. The only specific factor influencing daytime sleepiness in HIV infected patients is probably treatment with HAART. The most important factor determining sleepiness and sleep quality in HIV infected patients is depression which was found to be independent from the immunological state and HAART of the patients.

Introduction

Sleep disturbances, daytime sleepiness, and fatigue are common complaints among patients with HIV infection. In previous studies, daytime sleepiness [1], fatigue [2,3], insomnia [4–6], and other sleep disorders such as restless legs syndrome (RLS) [7] or obstructive sleep apnea syndrome [8] have been described in up to 70%. However, these studies described an epidemiological association. There is no consistent data on the link between the immune state of HIV infected patients and their sleep problems although such a link has been reported in earlier studies by means of polysomnography [9]. Sleep disturbances can cause severe impairment in quality of life and can even affect the adherence of the patients to antiretroviral treatment.

Early polysomnographic studies revealed longer sleep onset latency, shorter total sleep time, reduced sleep efficiency, more time spent awake and in stage 1 in HIV infected patients [10]. REM latency was slightly reduced and correlated negatively with depressive symptomatology, while percentages of REM and slow wave sleep were normal [10]. These findings were independent from the immune state of the patients in most studies [4,9,10]. As one possible mechanism, disturbed nightly TNF-alpha and growth hormone metabolism had been suggested [11,12].

We were interested in the association of the immune state of HIV infected patients and of other aspects of the infection such as medical treatment and cognitive disturbances and their sleepiness and sleep quality as measured by standardized questionnaires.

In particular, we assumed that sleep quality can be affected by different changes which might occur during HIV infection such as immunological parameters, treatment, psychosocial problems, and comorbid disorders. In particular, psychosocial problems can cause depression and, thus, may also cause sleep impairment which is one major symptom of depression in many sufferers.

Therefore, we performed a cross sectional study by evaluating sleepiness and sleep quality in HIV infected patients and also registered their actual immune state. Our hypothesis was that an increased deterioration of the immune state in HIV infected patients is associated with an increased daytime sleepiness and a decreased sleep quality.

Methods

A standardized questionnaire was handed out to 180 consecutive HIV-infected Caucasian patients referred to the HIV outpatient clinics at the Department of Neurology and at the Department of Internal Medicine, University of Münster, Germany. These two departments serve as supraregional referral centres for people with HIV infection. Referral does not necessarily mean that there were internal or

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neurological problems or disorders. The majority of patients were referred for routine control investigations (i.e., regular control of viral load and CD4+ cell count, screening for subclinical neurological manifestations such as neuropathy).

All HIV infected patients had to fulfil the following inclusion criteria: age > 18 years; being able to fill in the questionnaire (at least with the help of the physician or the clinic nurse); confirmed HIV infection. HIV infection was proven with an ELISA and, if positive, confirmed with a Western-blot analysis. 120 age- and sex-matched Caucasian control subjects aged > 18 years without a history of neurological or psychiatric disorders and clinically non-demented were recruited from waiting relatives of surgical patients at the trauma outpatient clinic at the University Hospital. The control subjects were not specifically tested for HIV infection but were asked whether they had a test in the past and whether they belong to a risk population for HIV infection. We recorded demographic and disease-specific data ($CD4^+$ cell count, viral load, stage of HIV infection according to the Centers of Disease Control [13]); viral load below the limit of quantification was set as 0. We also registered intake of highly active antiretroviral treatment (HAART). Intake of efavirenz was an exclusion criterion because this drug is known to cause severe sleep disturbances [6]. The presence of cerebral opportunistic infections (i.e., toxoplasmosis, progressive multifocal leukencephalopathy, cryptococcosis, lymphoma, and tuberculosis) was evaluated by neuroimaging and appropriate diagnostic work-up including clinical screening for dementia, MRI, EEG, and other neurophysiological examinations in all patients. The diagnosis of an HIV associated neurocognitive disorder (HAND) was made according to the published international criteria [14] by neuropsychological testing which belongs to the routine work-up in our department. We only enrolled patients without any neurocognitive problems and patients with aysmptomatic neurocognitive impairment (ANI) or with mild neurocognitive disorder (MND); the latter two diagnoses were combined as HAND in this study. AIDS dementia was an exclusion criterion.

Blood investigations (viral load and $CD4^+$ cell count) and clinical examinations were performed in all patients. Before participating in the study, all patients and control subjects gave written informed consent. The study was approved by the local ethics committee.

We used the Epworth Sleepiness Scale (ESS) [15] in a validated German version [16] in order to measure daytime sleepiness. The ESS results in a score between 0 and 24. A score above 9 is regarded as abnormal [15,17] and was used in our study to identify the percentage of patients or control subjects with abnormal daytime sleepiness. In addition, we used the Pittsburgh Sleep Quality Index (PSQI) [18] in a validated German version [19] which is a measure for sleep quality and results in a total score (maximum 21) consisting of seven domains (see Table 2). A total score above 5 is regarded as a marker of poor sleep quality. We used this cut-off to identify the percentage of HIV infected patients or control subjects with a significantly decreased sleep quality. Further, we used the Beck's Depression Inventory (BDI) to evaluate comorbid depressive state [20]. The BDI is a self measure of depression and has been validated as a reliable tool to diagnose the severity of depressive symptoms but not to make the final diagnosis of depression. We used the latest validated German Version (BDI-2) [21]. In this German version, the maximum total score is 63, a score higher than 8 but lower than 14 is regarded as mild depressive symptoms, a score higher 28 is regarded as severe depression (without making a diagnosis of depression according to ICD-10 or DSM-III). We also used the cut-offs of 8 (up to 14) and 28 in order to identify the subgroups of mildly depressed patients and severely depressed patients, respectively.

Since most of the data do not follow a normal distribution, we used the non-parametric Mann–Whitney-*U*-test to explore whether there were significant differences in quantitative data between groups. Chi square test and Fisher's exact test were used for the analysis of qualitative data. Correlations were calculated using Spearman rank test. Because of multiple comparisons, significance level was set at $p = 0.01$.

Table 1
Demographic data of the HIV infected patients and control subjects. Data are presented as arithmetic mean with standard deviation or as percentage. Statistical comparison by non-parametric testing.

		HIV infected patients control group		p value
		(n = 180)	(n = 120)	
Sex	Female	12.2%	16.7%	0.227
	Male	87.8%	83.3%	0.148
Age (years)		44.1 +/− 9.2	42.9 +/− 12.8	0.041
Body mass index		23.1 +/− 3.1	23.7 +/− 2.8	
CDC stage	1	7.3%	-	
	2	32.1%	-	
	3	60.6%	-	
CDC stage	A	15.9%	-	
	B	40.9%	-	
	C	43.3%	-	
Viral load (per μl)		48,245 +/− 121,163	-	
CD4+ cell count (per μl)		404 +/− 288	-	
HAART[a]		84.8%	-	
HAND[b]		24.1%	-	
Cerebral opportunistic infection		16.8%	-	

[a] Denotes highly active antiretroviral treatment.
[b] Denotes HIV associated neurocognitive disorder (both ANI and MND).

Results

The demographic and clinical data of the patients and of the control group are presented in Table 1. We observed a trend towards a slightly lower BMI in HIV infected patients as compared to our control group. No significant differences could be detected. The immune parameters of the HIV infected patients were within the expected range of a typical clinical sample, 47.1% of the patients had an HIV viral load below the limit of quantification.

In Table 2, the data of the ESS, the PSQI, and the BDI are presented separately for the HIV infected patients and the control group. Except for the sleep duration (domain 3 of the PSQI), all parameters measured in this study showed highly significant differences between HIV infected patients and control subjects. Daytime sleepiness was significantly increased (46.6% versus 19.4%; $p < 0.001$), and sleep quality was significantly decreased in HIV infected patients, also the percentage of patients with abnormal sleepiness or sleep quality was significantly higher (63.9% versus 21.0%; $p < 0.001$). Further, HIV infected patients showed a significantly higher score in the BDI and a higher percentage of both patients with mild depressive symptoms and a manifest depression.

We then divided that HIV infected patients into subgroups. First, the patients without and with abnormal daytime sleepiness (i.e., Epworth sleepiness scale score > 9) were compared (Table 3). We observed a trend towards a lower viral load and towards a higher percentage of HAART intake in those patients with abnormal daytime sleepiness; in the latter patients we also observed a significantly higher BDI score and a significantly higher percentage of patients with mild depressive symptoms but not severe depression. No further significant differences with respect to the immune state were observed between the two patients groups. Second, the patients with and without poor sleep quality (i.e., PSQI score > 5) were compared (Table 4). Again, we found a significant difference in the BDI score and in the percentage of patients without and with poor sleep

Table 2
Sleepiness and sleep quality of HIV infected patients and control subjects. Data are presented as arithmetic mean with standard deviation or as percentage. Statistical comparison by non-parametric testing including Chi square test.

	HIV infected patients control group		p value
	(n = 180)	(n = 120)	
Epworth sleepiness scale	9.4 +/− 4.9	6.5 +/− 3.2	<0.001
score > 9	46.6%	19.4%	<0.001
PSQI[a] 1(subjective sleep quality)	1.4 +/− 0.8	0.7 +/− 0.6	<0.001
PSQI 2 (sleep latency)	1.3 +/− 1.0	0.7 +/− 0.8	<0.001
PSQI 3 (sleep duration)	0.8 +/− 1.0	0.6 +/− 0.8	0.087
PSQI 4 (sleep efficiency)	1.4 +/− 0.7	0.9 +/− 0.4	<0.001
PSQI 5 (sleep disturbance)	1.1 +/− 1.1	0.4 +/− 0.8	<0.001
PSQI 6 (needs medication)	0.6 +/− 1.1	0.1 +/− 0.3	<0.001
PSQI 7 (day dysfunction)	1.4 +/− 0.9	0.7 +/− 0.6	<0.001
PSQI total	8.0 +/− 4.4	4.1 +/− 2.5	<0.001
score > 5	63.9%	21.0%	<0.001
BDI[b]	13.9 +/− 10.7	3.7 +/− 4.1	<0.001
score > 8	63.5%	12.6%	<0.001
score > 28	10.8%	0%	<0.001

[a] Denotes Pittsburgh Sleep Quality Index.
[b] Denotes Beck's Depression Inventory.