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Sleep Disturbances in Men with Asymptomatic Human Immunodeficiency (HIV) Infection

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Summary: During the clinical latency phase of human immunodeficiency virus (HIV) disease the central nervous system may be infected and begin to manifest subtle dysfunction. Our early investigations demonstrated persistent alterations in the sleep architecture of HIV-infected asymptomatic men. The major aims of this study were to delineate alterations of sleep architecture in asymptomatic HIV-infected men, to identify and describe sleep behavior complaints and to seek a correlation between objective sleep parameters and subjective complaints of sleep behavior. The study sample consisted of 24 men, 14 HIV-infected and 10 HIV-negative, age-matched controls. The protocol included a comprehensive history and physical, two polysomnograms, urine toxicity, detailed written sleep questionnaire, the Pittsburgh Sleep Quality Index, the Spielberger State–Trait Anxiety Test and the Beck Depression Inventory. Our results indicated that sleep architecture differed from controls in that wakefulness, slow-wave sleep [SWS—stage 3 and 4 nonrapid eye movement (NREM) sleep] and stage rapid eye movement (REM) sleep were more evenly dispersed throughout the night. In particular, SWS was prevalent during the second half of recorded sleep. The observed changes in the NREM/REM cycle could not be explained on the basis of underlying psychopathology. Just as the course of individuals with HIV infection varies, it is expected that sleep abnormalities will vary. Considering the known relationships between NREM stage 3 and 4 and immune system function, it is possible that the observed alterations in the NREM/REM cycle are related to coincident changes in immunologic function. Quantitative measures of NREM sleep, especially SWS and REM sleep, are perhaps of greater significance than relative measures of sleep stages. The relationship of sleep architecture alterations to circadian rhythms also requires investigation. **Key Words:** HIV infection—Sleep disturbances.

It has been well established that there is a lag time between initial human immunodeficiency virus (HIV) infection and the development of the clinical syndrome known as the acquired immunodeficiency syndrome (AIDS). This lag time has been termed clinical latency. It is during this clinical latency phase that the central nervous system (CNS) may be infected and begin to manifest subtle dysfunction due to HIV (1). Recently, Koralnik et al. reported that electrophysiologic tests may be the most sensitive indicators of subclinical neurologic injury in otherwise clinically asymptomatic HIV-infected individuals (2). CNS involvement eventually results in serious neurological dysfunction in the majority of individuals with AIDS (3).

Sleep electroencephalographic (EEG) disturbances have been reported in HIV-infected individuals at different stages of HIV disease progression (4–8). Previously altered sleep patterns have been reported in animal experiments, in response to acute infections. Toth and Krueger observed an initial enhancement of slow-wave sleep (SWS) nonrapid eye movement (NREM), followed by an inhibition of NREM sleep in rabbits. These experiments showed a marked time-dependent alteration in sleep stages after microbial inoculation, which varied temporally depending on the organism delivered (9).

Investigations by Norman and colleagues have demonstrated persistent alterations in the sleep architecture of HIV-infected asymptomatic men when compared to normative data (10). Specifically, a distortion in NREM/REM sleep cycles, an increase in the total percent of SWS and the placement of SWS in the terminal sleep cycles was described (10). The reported sleep alterations have not been explained on the basis of sleep deprivation, chronic drug use, anxiety or depression. The major aims of this study were 1) to delineate alterations of sleep architecture in asympto-

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TABLE 1. *Polysomnogram results: HIV-infected homosexual men compared to HIV-negative male controls and normative published mean data*

Sleep parameter	HIV-infected asyptomatic mean (±SD) (n = 14)	HIV-negative controls mean (±SD) (n = 10)	Normative data mean (±SD)[a]
Total sleep time (minutes)	404.9 (53.6)	403.2 (58.2)	435.0 (44.6)
% Sleep efficiency	92.2 (4.9)	93.6 (4.0)	96.0 (7.0)*
Absolute minutes SWS	92.9 (33.6)	82.1 (28.0)	69.6 (NP)**
% Stage 2	43.9 (8.4)	45.9 (8.4)	57.0 (8.8)*
% Total SWS	22.8 (6.9)	20.6 (7.5)	16.0 (NP)*
% REM sleep	21.7 (5.9)	24.2 (4.8)	24.0 (3.6)
% SWS 1st ½	33.1 (8.5)	29.8 (12.6)	(NP)
% SWS 2nd ½	12.0 (7.2)	9.8 (8.6)	(NP)
Latency to stage 2	5.6 (8.4)	8.4 (10.7)	5.0 (10.5)
REM latency	79.0 (22.5)	106.8 (32.5)	86.0 (38.1)
SWS latency	21.1 (18.0)	28.3 (24.5)	30.0 (NP)
Number of REM periods	6.3 (3.1)	4.6 (1.6)	4.5 (0.7)**
Average REM period duration	17.6 (7.8)	22.5 (6.3)	29.0 (5.0)
Number of sleep stages	47.8 (16.1)	41.7 (8.1)	40.0 (NP)
Number of awakenings	8.5 (5.2)	7.2 (3.2)	3.5 (NP)*
Number of stage 1 shifts	16.1 (7.2)	12.9 (4.3)	9.5 (NP)*

[a] Published normative data (14); *$p \leq 0.01$; **$p < 0.05$ as compared to the HIV-infected group only.

matic HIV-infected men; 2) to identify and describe sleep/wake behavior complaints in this group; and 3) to seek a correlation between objective sleep parameters and subjective complaints of sleep/wake behavior.

METHODS

All subjects signed an informed consent at the time of their initial interview. The protocol included 1) an interview with an experienced sleep disorders specialist; 2) two polysomnograms (PSGs); 3) urine toxicity screening for narcotics, hypnotics, recreational drugs, tranquilizers and alcohol—collected at the initial interview and again on the night of the second PSG; 4) a detailed written sleep questionnaire; 5) the Pittsburgh Sleep Quality Index (PSQI); 6) the Spielberger State–Trait Anxiety Tests (STAI); 7) the Beck Depression Inventory (BDI); and 8) a physical examination by a Physician's Assistant, trained in HIV disease diagnosis to assure asymptomatic status in the HIV-infected men.

PSG measured breathing pattern (Respigraph®), heart rate and rhythm, arterial oxygen saturation (BIOX oximeter), sleep stages (central EEG, electrooculography and digastric electromyography) and limb movements (anterior tibialis electromyography). The first PSG (PSG1) was used to eliminate "first night effect" and to rule out coincident underlying sleep pathology (obstructive sleep apnea, parasomnias or periodic limb movements during sleep). The second night PSG (PSG2) was used in the final data analysis.

The following sleep parameters were analyzed from PSG2: total sleep time (TST), sleep efficiency index percent (SEI%); sleep latency to stages 1, 2, REM sleep and SWS (defined as sleep stages 3 and 4); number of stage 1 shifts; number of sleep stages; number of awakenings; average REM period duration (minutes); number of REM periods; total percent stage 2 sleep, SWS and REM sleep; percent SWS in first half of the night, percent SWS in the second half of the night; and absolute minutes of SWS (ABSSWS) for the entire night. PSGs were hand-scored according to the standard cri-

TABLE 2. *Sleep parameters in HIV-infected and HIV-negative men: all values are percentage of group exhibiting abnormality*

	SEI[a] <90	>6 Awakenings	TSWS[b] >17	SWS present in terminal sleep cycles	Distorted NREM/REM cycles[c]	Subjective sleep complaints
HIV-infected (n = 14)	29	64	71	71	71	86
HIV-negative (n = 10)	10	50	60	40	30	10

[a] SEI: sleep efficiency index.
[b] TSWS: total slow wave sleep percent.
[c] Absence of normal NREM/REM sleep cycles across the night.

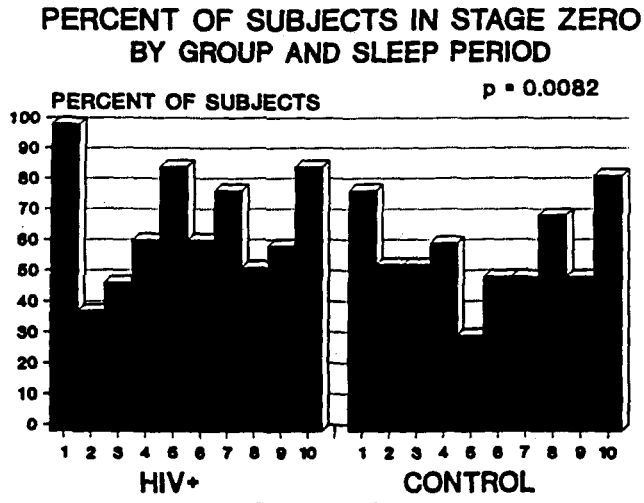

FIG. 1.

teria of Rechtschaffen and Kales (11). The presence of alpha-NREM anomaly and cardiac arrhythmias was also evaluated.

The normal temporal distribution of sleep stages in adults (ages 17–50) has been well documented: 1) NREM sleep episodes recur in bouts or epochs, separated by REM sleep periods. 2) Each consecutive NREM/REM cycle demonstrates a decrease in the amount of SWS, wherein most SWS occurs during the first, second or third NREM sleep periods, usually in the first half of the night. 3) REM sleep periods cycle approximately every 90–100 minutes, and each subsequent REM period is longer in duration (12). In this paper, we term the periodic cycling of NREM and REM sleep the NREM/REM sleep cycle. Alterations in the NREM/REM cycle were defined by a sleep pattern that differed in an obvious manner from the expected temporal distribution of NREM/REM sleep described above.

Sample

Thirty-four male subjects were interviewed. Protocol exclusion criteria included a history of AIDS-related complex or a diagnosis of AIDS; a history of major medical, neurologic or psychiatric illness; regular use of antidepressants, hypnotics, tranquilizers, narcotics or alcohol; a history of intravenous drug abuse; chronic pain syndrome; or past/present treatment with Zidovudine (AZT).

Ten subjects were eliminated from the final data analysis. Reasons for exclusion included: presence of obstructive sleep apnea (apnea/hypopnea index = 8), one subject; lack of HIV-negative serology confirmation, one subject; positive urine drug toxicity, two subjects; intravenous drug abuse and alcoholism, one subject; inability to sleep in the laboratory, one subject; past and present psychiatric history, one subject; and noncompliance with protocol, three subjects.

The final study sample consisted of 14 HIV-infected asymptomatic homosexual and 10 HIV-negative (6 heterosexual and 4 homosexual) men. Two subjects, one from each group, were unable to have two sleep studies. This was due to technical (scheduling) problems between the sleep laboratory and the subjects' work schedules. With the exception of these two subjects, the remaining subjects underwent two nights of PSG.

Data analysis

All PSGs were scored by a registered polysomnographic technologist and reviewed by an accredited clinical polysomnographer (A.C.P.), both of whom were not informed of the subjects' HIV status.

In order to better interpret the previously reported distortion in NREM/REM cycles (6,10) and to make a global analysis of the patterns of sleep between HIV-infected and control subjects, the total sleep time (TST) was divided into 10 equal periods of elapsed time. Within each period, each stage of sleep was scored as either present or absent. That is, one or more appearances of a stage within a period would mark that stage as present for that period. Otherwise, the stage was marked as absent.

For each subject and sleep stage, the data were arranged in a matrix of zeros and ones, where rows were individual subjects and columns were sleep periods. The Cochran Q test for independence (13) was computed for each group separately and for all subjects combined. The difference between the sum of the individual Q statistics and the Q statistic for the whole

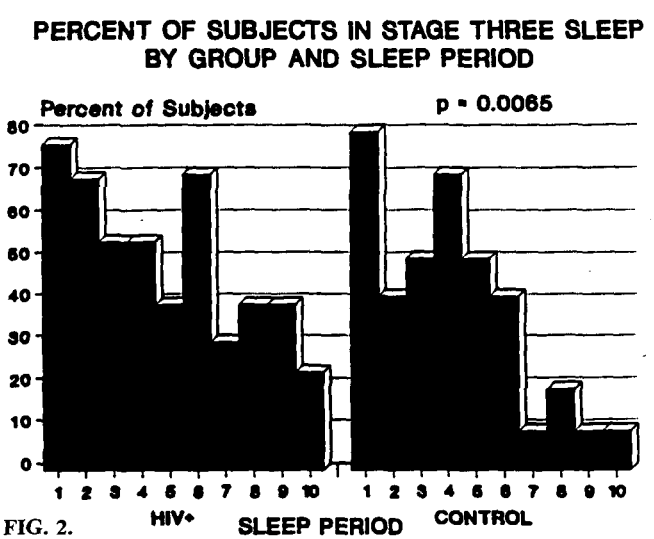

FIG. 2.

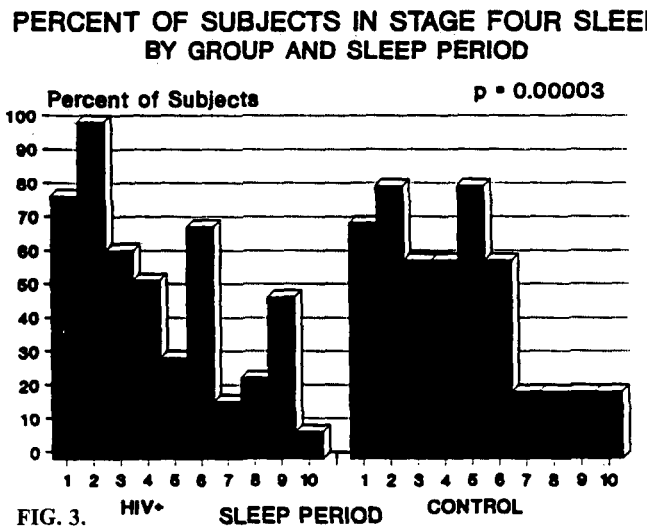

FIG. 3.

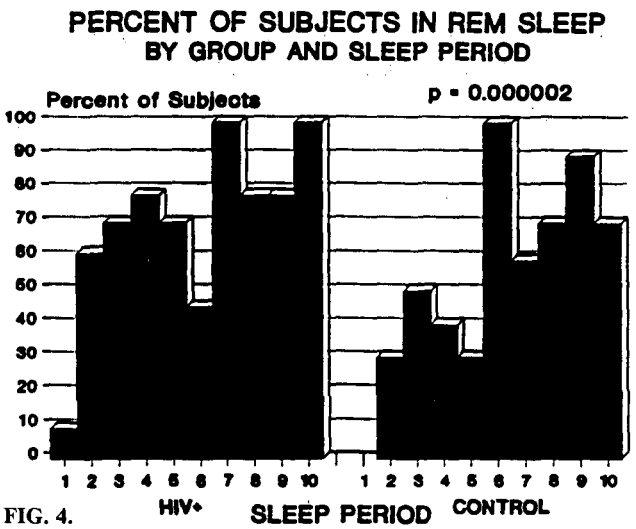

FIG. 4.

group was compared to the appropriate tabulated chi-square for a test of the equality of responses between groups.

The two nights of PSG recording were compared using the Levene F test for variability and the Mann–Whitney rank sum test. A one-way analysis of variance (ANOVA) was used to analyze the sleep parameter mean data and the Bonferroni T test was used to determine differences between means when differences were indicated by ANOVA.

RESULTS

No difference in age was found between groups [HIV-infected age mean = 36.2 (±7.6), range = 26–50; HIV-negative age mean = 32.9 (±5.5), range = 24–42]. Polysomnographic results as compared to normative published data are presented in Table 1.

The only significant difference in mean sleep parameter data in comparing PSG1 to PSG2 was observed in the number of stage 1 shifts. A significant decrease in stage 1 shifts on the second recording was observed [PSG1 mean = 19.8 (±7.3); PSG2 mean = 12.8 (±4.6); $p < 0.05$]. Variations in objective sleep parameters and subjective sleep complaints between the two groups are shown in Table 2.

Using the Cochran Q analysis, it appeared that the HIV-infected subjects were more frequently in stage zero (awake) than were the controls. The dip in frequency of stage zero among controls was absent in the HIV-infected group (Fig. 1). HIV-infected subjects had a generally higher profile for stage 3 sleep than the controls and they did not show as much of a decrease in the last half of the TST (Fig. 2). Stage 4 sleep persisted as the night progressed in HIV-infected subjects, the controls appeared to have a dichotomous pattern, i.e. frequent stage 4 in the first half of the night, and nearly absent stage 4 in the second half (Fig. 3). Controls illustrated the expected biphasic pattern of REM sleep, with low REM sleep during the first half of the TST. The HIV-infected subjects were more likely to be found in REM sleep throughout the TST (Fig. 4). This analysis demonstrated that the two groups differed significantly in sleep stage zero (awake), stage 3 and stage 4 sleep and REM sleep ($p < 0.01$). There were no significant differences observed between the groups for stages 1 or 2 sleep (Figs. 5 and 6).

Subjective sleep complaints and psychometric test results

The psychometric test results [mean (±SD)] and subjective complaints (as a percent of the group) are presented in Table 3.

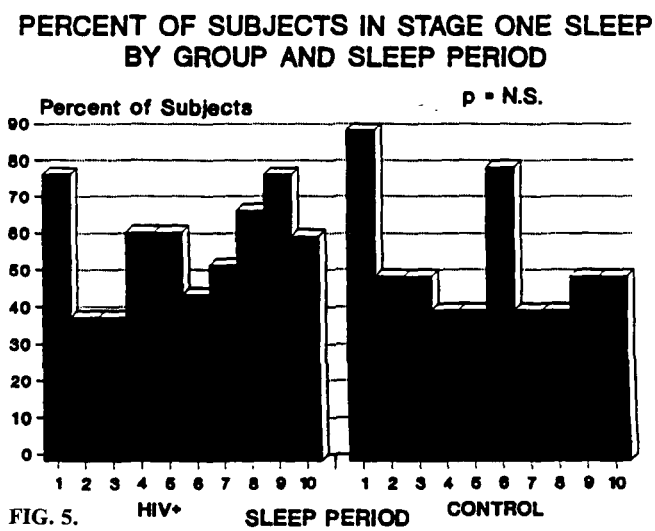

FIG. 5.

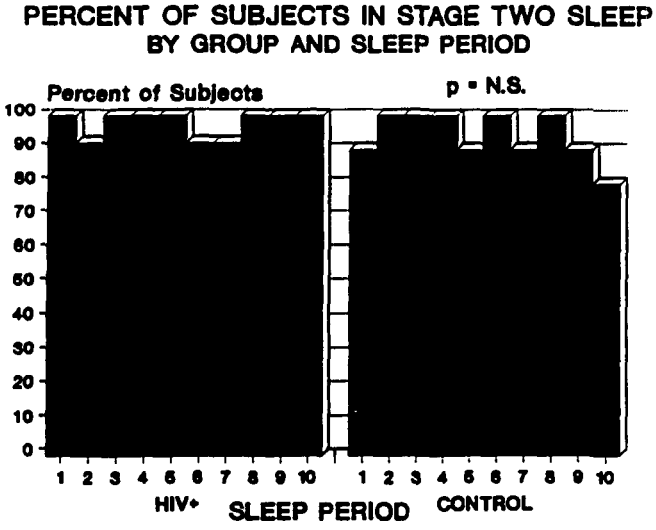

FIG. 6. Percentage of subjects in stage 2 sleep by group and sleep period.

DISCUSSION

We analyzed the sleep architecture of 14 HIV-infected asymptomatic homosexual men and compared it to 10 HIV-negative, age- and sex-matched controls. Our observations indicate that there are differences in the sleep architecture of HIV-infected asymptomatic individuals as compared to age-matched controls. Sleep architecture in HIV-infected asymptomatic homosexual men differs from controls in that wakefulness, stage 3 and 4 NREM sleep and REM sleep appeared to be more evenly dispersed throughout the night. In particular, SWS was prevalent during the second half of recorded sleep.

The observed alterations of sleep architecture cannot be explained on the basis of underlying psychopathology. Although the Beck Depression Inventory showed a significantly higher mean score in the HIV-infected group, this score is still below the limit for mild depression (15). Other psychometric tests were similar between the two groups.

The PSQI showed a trend toward a significant increase in sleep-related complaints in the HIV-infected group ($p = 0.06$). This suggests that these individuals perceive greater sleep disturbances than our control group. Although there appeared to be a greater percentage of subjective complaints in the HIV-infected group for disorders of sleep initiation, sleep maintenance and daytime drowsiness, no correlation was observed between the subjective sleep complaints and the PSG-derived sleep parameters. This observation suggests that purely quantitative measures of sleep may not reflect sleep disturbances in this population and that qualitative assessments of sleep architecture, similar to those provided by the Cochran Q analysis, may correlate better with subjective sleep complaints.

REM sleep was distributed more uniformly across the night in HIV-infected homosexual men than in controls. The NREM/REM cycles in the HIV-infected group were often disrupted, a feature that would account for the observation detailed by the Cochran Q analysis of REM sleep distribution across the night. It is unlikely that distortion of the NREM/REM cycle represents a specific HIV-related phenomenon, as 30% of the controls also showed this pattern.

Quantitative differences in NREM stage 3/4 sleep between HIV-infected asymptomatic homosexual men and normative data have been reported previously (4). However, in comparison to controls no such relationship was found in this study. The control group had values of SWS positioned between normative data and the HIV-infected group (Table 1). The sample size may have been too small to statistically detect quantitative differences in sleep parameters. Nonetheless, there were significant differences in the distribution of SWS across the night, and SWS in the terminal sleep cycles was observed in nearly twice as many subjects in the HIV-infected group (Table 2 and Figs. 2 and 3).

Longitudinal observations in HIV-infected men suggest quantitative changes in SWS. Not all HIV-infected men in this sample presented with similar sleep complaints or sleep architecture abnormalities on PSG. It is suspected that these findings may be partially explained by the varied "time of initial infection" among the study group. It was not possible to determine how long these HIV-infected men had been seropositive,

TABLE 3. *Psychometric test results and subjective sleep complaints*

	DIMS[a] (%)	DOES[b] (%)	State anxiety (±SD)	Trait anxiety (±SD)	BDI[c] (±SD)	PSQI[d] (±SD)
HIV-negative (n = 10)	10	10	27.3 (9.9)	29.2 (6.5)	1.0* (2.0)	2.4 (1.2)
HIV-infected (n = 14)	57	43	30.1 (8.2)	34.8 (7.8)	3.3 (3.6)	3.5 (1.9)

[a] DIMS: complaints of initiating or maintaining sleep.
[b] DOES: complaints of daytime drowsiness and/or fatigue.
[c] BDI: Beck Depression Inventory; *$p < 0.05$.
[d] PSQI: Pittsburgh Sleep Quality Index.

therefore, all clinical and laboratory observations must be understood to represent many different points in time (i.e. along the continuum of HIV disease). Just as the course of individuals with HIV infection varies, it is expected that sleep abnormalities will vary. Quantitative measures of NREM sleep, especially SWS and REM sleep, are perhaps of greater significance than relative measures of sleep stages.

Considering the known relationships between SWS and immune system function, it is attractive to link alterations of these sleep stages to immune status (16–18). The data presented herein, although suggesting an association between immune mediators and sleep, need additional parameters of assessment before a true liaison can be substantiated. The relationship of sleep architecture alterations to circadian rhythms also needs to be investigated.

In conclusion, electrophysiologic tests may be the most sensitive indicators of subclinical neurologic involvement with HIV infection, and some of the observed sleep EEG alterations may be related to primary CNS involvement with HIV (2). However, the precise etiology for our observations remains unclear, and additional studies are warranted for a disease of this severity and prevalence.

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