
Disease severity, scratching, and sleep quality in patients with atopic dermatitis

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Background: The relationship between sleep quality and disease severity in patients with atopic dermatitis has not been clearly defined.

Methods: Sleep efficiency and scratching were measured over 2 nights by polysomnography, actigraphy, and self-report in 20 adults with atopic dermatitis. Tumor necrosis factor, interleukin (IL)-6, and IL-10 were assayed from a subset of 9 participants.

Results: Sleep measured by actigraphy and polysomnography were strongly associated with each other. Decreased sleep efficiency was associated with increasing disease severity, scratching, and IL-6. Self-reported sleep quality and quality of life were not significantly correlated with either objective sleep measure.

Limitations: Results in this pilot study await confirmation in a larger investigation.

Conclusion: Objective measures but not self-report documented that increasing severity of atopic dermatitis results in more scratching and declining sleep quality. Our data also suggest an important relationship between sleep and IL-6. (J Am Acad Dermatol 2008;58:415-20.)

Atopic dermatitis (AD) is an inflammatory skin disease¹ that occurs in up to 20% of the population²⁻⁴ and can significantly compromise quality of life as patients struggle with fragmented sleep, embarrassment, emotional distress, and impaired social functioning. Compromised sleep that accompanies nighttime scratching can lead to daytime fatigue, mood disorder, and poor school or work performance.⁵⁻⁸ Few studies of sleep in patients with AD have used polysomnography (PSG), instead relying primarily on self-report and actigraphy, and producing results that are potentially inconsistent and fail to clearly define an association between the disease and sleep. The purpose of this

Abbreviations used:

AD: atopic dermatitis
IL: interleukin
PSG: polysomnography
REM: rapid eye movement
TBSA: total body surface area

investigation was to establish the relationship between sleep quality and AD disease severity, using 3 measures of sleep: PSG, actigraphy, and self-report.

METHODS

Participants

Participants were included if they were between 18 and 65 years of age and had mild to moderate AD, as defined by Hanifin,⁹ affecting at least 5% of total body surface area (TBSA) (estimated using the area of participant's palm of the hand, including fingers, as approximately 1% TBSA). Participants were excluded if they: had failed other systemic and/or topical immunosuppressive agents such as tacrolimus, methotrexate, or cyclosporine; had received therapy for insomnia within 4 weeks before the baseline visit; were, in the opinion of the investigator, known to be unreliable or noncompliant with

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medical treatment or appointments; had drug abuse problems, mental health dysfunction, or other factors limiting their ability to cooperate fully; were taking antihistamines, oral immunosuppressant medication, or antidepressant medication; or had any other condition or earlier/current treatment which, in the opinion of the investigator, would render the participant ineligible for the study.

Procedures

All participants were seen for a screening visit and two study visits. At screening, participants were interviewed and excluded if they reported evidence of current depression or sleep disorder, or treatment with an antidepressive, sleep, antihistamine, or oral immunosuppressant medication. Participants who, at the initial PSG, were found to have sleep apnea, restless leg syndrome, or other sleep-related disorders were also excluded from the study. Study visit evaluations included PSG, actigraphy, blood draw, and self-report questionnaires inquiring about sleep quality, itch, and the impact of AD and sleep difficulty on quality of life. A nurse or physician assessed TBSA.

Polysomnography. Participants received two consecutive overnight PSGs. PSGs were recorded using software (Alice 3, Version 1.20, Respironics, Murrysville, Pa) and included the following physiologic parameters: electroencephalogram (C4/A1, C3/A2, O1/A2); bilateral electro-oculogram; submental and extensor digitorum electromyograms; electrocardiogram (modified V₂ lead); oronasal pressure/thermistor sensors; piezo-crystal respiratory belts; snoring microphone; position sensor; and oxygen saturation via pulse oximetry (Nellcor, Boulder, Colo). The initial study was used as an acclimatization night, followed by full data acquisition and analysis on the second night. Studies were scored using sleep staging criteria defined by Rechtschaffen and Kales.¹⁰ PSG data used for this investigation included sleep latency (time to sleep onset), sleep efficiency (ratio of total sleep time to time in bed), and percent of sleep time in rapid eye movement (REM) and stages 1 through 4.

Scratching index. Participants were videotaped during PSG. The sleep technician observed and recorded each time period in which scratching occurred. A scratching event was recorded as such when a burst of electromyographic activity of at least 3 seconds was accompanied by a visible scratching motion.

Actigraphy. The Actigraph Motionlogger (Ambulatory Monitoring Inc, Ardsley, NY) was used to assess periods of sleep and wakefulness.¹¹⁻¹³ The actigraph, which has the appearance of a wristwatch, produces a piezoelectric bimorph-ceramic cantilevered

beam that generates voltage each time the actigraph is moved. With frequency of movement selected as a collection mode in this study, each time the movement signal crossed a threshold set to correspond with about 0.01G of acceleration, a counter was incremented. Thus, the actigraph recorded frequency and volume of movements throughout the night; software provided by the manufacturer in turn produced assessments of sleep latency, efficiency, and periods of awakening. Each participant wore the actigraph on their nondominant wrist through each night in the PSG laboratory. After an overnight stay in the PSG laboratory, the actigraph data were downloaded via an infrared docking station. Actigraph data used for this investigation included sleep latency (time to sleep onset) and efficiency (proportion of time in bed spent asleep), activity mean (average number of activity episodes), wake episodes (average awakenings), and longest sleep episode (longest period of sleep).

Questionnaires

Dermatology life quality index. The 10-item Dermatology Life Quality Index¹⁴ is a commonly used questionnaire on which the patient quantifies the impact of AD on life (eg, "How embarrassed or self-conscious have you been because of your skin?").

Itch rating. The itch rating was obtained by using a visual analog scale consisting of a 100-mm line on which the patient indicated a point between "worst itch imaginable" and "no itch."

Cytokine assays. During the second night of PSG, blood was drawn in the evening before PSG and on the following morning on awakening. With each sample, 10 mL of heparinized blood was collected. Peripheral blood mononuclear cells were isolated using the Accuspin (Sigma, St Louis, Mo) tube method allowing for the collection of plasma before removing the cell layer. The plasma was stored at -80°C in 1-mL aliquots. Peripheral blood mononuclear cells were harvested and washed 3 times with phosphate-buffered saline before cell stimulation. Cells were cultured at 1×10^6 cells in 1 mL of Roswell Park Memorial Institute complete medium (+10% fetal calf serum, + pen/strep, + glutamine) unstimulated or stimulated with 20 ng/mL of anti-CD3 per well for 48 hours at 37°C + 5% carbon dioxide. The wells were then harvested and centrifuged. The supernatants were removed and stored at -80°C until assayed by enzyme-linked immunosorbent assay for interleukin (IL)-6, IL-10, and tumor necrosis factor- α . The cell pellets were resuspended in RNA lysis buffer (Qiagen, Valencia, Calif) plus mercaptoethanol and stored at -80°C.

Table I. Spearman correlations of actigraphy with scratching index and polysomnography

Actigraphy	Scratching		Polysomnography			
	Scratch index		Sleep latency		Sleep efficiency	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Sleep latency	−0.104	.662	0.606	.005	−0.035	.884
Sleep efficiency	−0.519	.019	−0.384	.095	0.442	.050
Activity mean	0.518	.019	0.513	.021	0.460	.041
Wake episodes	0.305	.191	0.603	.005	−0.390	.084
Longest wake episode	0.305	.191	0.326	.161	−0.400	.134
Longest sleep episode	0.355	.125	−0.545	.013	0.535	.015

Data analyses

All statistical analyses were performed with software (JMP, SAS Institute Inc, Cary, NC). Tables I and II contain Spearman nonparametric correlation coefficients and their associated *P* values. An analysis of variance using Dunnett test was used for comparing the control group, REM, with other sleep stages in terms of proportion of time spent scratching.

RESULTS

Eighteen of 20 participants were younger than 50 years, and 13 were female. Results are described by category of measure.

Comparison of PSG and actigraphy sleep measures

Two objective measures, PSG and actigraphy, documented sleep quality. To evaluate the degree of agreement between these two measures, linear associations between PSG and actigraphy sleep measures were assessed. Although PSG can provide detail not measured by actigraphy, the primary sleep outcomes, sleep latency (time elapsed between going to bed and falling asleep) and efficiency (total time asleep divided by total time in bed), were strongly associated. Sleep latency measured by actigraphy was correlated with PSG latency (0.61, *P* = .005), and sleep efficiency measured by actigraphy was correlated with PSG efficiency (0.44, *P* = .050) (Table I).

Scratching events

All scratching events occurred only during sustained wakefulness or in association with arousal or awakening from sleep. However, scratching episodes were assigned to the specific sleep stage maintained during the 90 seconds immediately before each scratch event/arousal. Mean minutes spent sleeping and scratching in each sleep stage are included in Fig 1. On average, participants spent a

Table II. Spearman correlations of sleep efficiency with skin, and sleep self-rating

	Polysomnography		Actigraphy	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Skin ratings				
Rajka and Langeland score	−0.422	.064	−0.345	.135
Total body surface area	−0.344	.137	−0.475	.034
Scratching index	−0.563	.010	−0.519	.019
Pittsburgh Sleep Quality Index	−0.002	.995	−0.298	.203
Dermatology Quality of Life Index	−0.364	.115	−0.082	.732

greater proportion of time scratching in stages 1 (*P* = .0074) and 2 (*P* < .0001) than in 3, 4, or REM. Scratching in REM sleep occurred only with arousal from sleep.

Scratching frequency related to disease severity and sleep quality

To determine how scratching is related to variation in skin condition and sleep quality, associations between scratching and self-rated itch, percent body surface, and sleep measurement were examined. Overall, scratching increased with increasing skin severity; as sleep improved, scratching decreased. Total scratching index was significantly correlated with percent TBSA (0.33, *P* = .008), PSG sleep efficiency (−0.56, *P* = .10), and actigraph sleep efficiency (−0.52, *P* = .019). However, objectively measured scratching did not correlate with the self-assessment itch rating.

Sleep change related to changes in disease severity and sleep self-rating

To determine how objectively measured sleep efficiency compares with sleep self-rating and how it is related to disease severity, associations between each measure were examined. PSG sleep efficiency

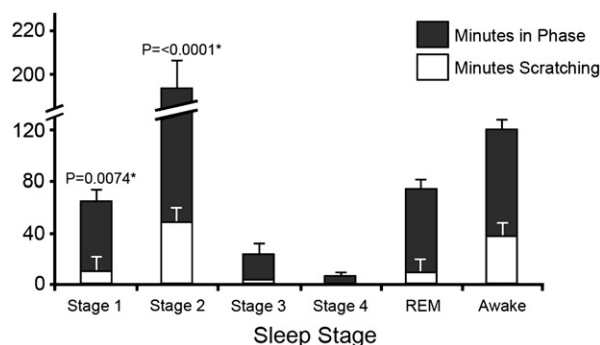


Fig 1. Sleep and scratch time in each sleep phase. REM, Rapid eye movement. *Proportion of time spent scratching in this stage was greater than in stage 3, stage 4, or REM.

was significantly correlated with the scratching index (-0.56 , $P = .010$) and the Rajka and Langeland skin score (0.42 , $P = .064$). Similarly, the actigraph sleep efficiency score correlated significantly with the dermatitis percent TBSA score (-0.48 , $P = .034$). The patient-completed Dermatology Life Quality Index did not correlate with either the PSG or the actigraph sleep efficiency scores (Table II).

Correlation of sleep efficiency with cell data

Cytokine production by peripheral blood mononuclear cells stimulated with anti-CD3, including tumor necrosis factor alpha, IL-6, and IL-10 were assayed from a subset of 9 study participants in an ancillary pilot study intended to assess the relationship between sleep and inflammatory markers. PSG sleep efficiency correlated with IL-6 pg/mL in both the evening (-0.60 , $P = .086$) and morning (-0.63 , $P = .070$) in anti-CD3 treated cells. Actigraphy sleep efficiency correlated significantly with IL-6 pg/mL morning-evening change (-0.70 , $P = .036$) indicating that sleep improved as the differential between the evening and morning cytokine values increased.

DISCUSSION

Sleep quality was inversely associated with disease severity in this group of adult patients with AD. Greater disease severity was strongly associated with poorer sleep, with most scratching in this and other studies seen in stages 1 and 2.¹⁵⁻¹⁷ The experience of AD is clearly linked with sleep, and impact of both on patients' lives is significant. Because reduced sleep can result in impairment in daytime mood and performance, sleep loss secondary to AD may contribute to the psychologic distress associated with the disease.^{11,18} Sleep measurement, therefore, provides an important end point in the study of AD and its treatment.

Results from this study underscore the importance of including objective measures of sleep and scratching. Episodes of scratching were confirmed by both electromyographic and video recordings. Accuracy of sleep assessment as a disease-related event was measure dependent, with marked differences found between objective and subjective sleep measures. The absence of a correlation between self-assessed sleep and either actigraphy or PSG suggests that, although patients may sense that they have slept poorly or that their scratching woke them up, they may not be able to accurately judge how much or how well they have slept. We previously reported that actigraph-measured sleep discriminated more clearly between AD and control groups than self-assessment with the Pittsburgh Sleep Quality Index,¹³ and studies of children have similarly found that mothers' sleep assessments failed to correlate significantly with actigraphy¹⁹ or video recordings of sleep, movement, or scratching.²⁰ In short, patient-report measurement of sleep, the primary outcome variable in some sleep-related research, appears to be inadequate as a solitary means of sleep assessment in patients with AD.

A variety of subjective and objective measures have been used to evaluate sleep in patients with AD, producing inconsistent findings and failing to establish a clear relationship among disease severity, scratching, and sleep quality.^{13,19,21-26} This study revealed moderately strong correlations between actigraphy scores and both the scratching index and PSG scores, which included sleep latency, sleep efficiency, and stage-2 sleep. Although actigraphy has been presented both as a measure of scratching²⁰ and sleep,¹³ the study by Benjamin et al²⁰ revealed that actigraphy recordings were significantly and highly correlated with video-recording measures of sleep, scratching, and restlessness. This collective evidence suggests that the actigraph, which is an accelerometer that measures wrist movement, produces a score that captures restlessness. Because sleep, scratching, and wrist movements are all intercorrelated, the actigraph provides a reasonable approximation for measurement of both scratching and sleep. It cannot document scratching as accurately as videotaping patients or attaching transducers to their forearm or fingers. Likewise, it cannot measure sleep as accurately as PSG, and cannot provide the detail of PSG necessary to diagnose sleep disorders. Nonetheless, actigraphy provides a low-cost, unobtrusive global measure of sleep that is well accepted by patients and can be used for extended periods of time. Actigraphy demonstrated a linear association with PSG, skin condition, and scratching in patients with AD, indicating

applicability for clinical trials of AD.²⁷ Thus, actigraphy provides an objective sleep measure that can help evaluate the relative contribution of specific treatments to the improvement of AD-related quality of life.

Limited pilot data suggest that IL-6 production increases as sleep is decreased in patients with AD. Numerous cytokines, including IL-6, are involved in regulation of the immune system. The correlation of sleep to evening-to-morning increases in IL-6 (pg/mL) suggests benefit from sleep, but may also partially reflect circadian rhythm patterns known to associated with variation in IL-6 or itch mediators.^{28,29} Some cytokines also serve nonimmune functions such as regulation of central nervous system processes including modulation of mood, sexual behavior, and sleep. Morning IL-6 levels are negatively associated with sleep quality.³⁰ Sleep deprivation in healthy individuals increases IL-6 and subcutaneous injections of IL-6 increases REM sleep.³¹⁻³³ Other data suggest that the role of elevated IL-6 in regulating the sleep-wake cycle is stronger in organisms where infection is present.^{34,35} Disordered sleep may lead to alterations in immune functions, including production of IL-6, that in turn may adversely affect host resistance to infection and inflammatory disease progression.³¹ Determination of how IL-6 levels and sleep quality are interrelated, the relative degree to which sleep disturbance in patients with AD is caused by sensation of itch or increase in IL-6, and the impact of decreased sleep on expression of AD, are important objectives of future research with larger patient samples. Other cytokines have also been found to be functionally related to sleep, including IL-1 β and tumor necrosis factor- α but were not studied here.³⁶ Small sample size and absence of a control group in the current study are additional limitations, and further research is clearly needed to confirm, clarify, or refute these findings.

In summary, sleep quality decreases as AD severity increases. Sleep measurement augments the assessment of disease-related quality of life in AD research, and provides an important outcome variable in clinical trials. Self-report is a poor measure of sleep quality. In contrast, actigraphy provides a useful measure of sleep in patients with AD, with advantages that include cost-efficiency, unobtrusiveness, and a capacity to measure sleep over extended time periods. Pilot data showing that IL-6 is associated with sleep quality suggest the importance of measuring this and other inflammatory markers to better understand the relationship among disease, sleep, and inflammation in this population of patients.

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