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Sleep-wake disorders and dermatology

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Abstract Sleep is an active process that occupies about one-third of the lives of humans; however, there are relatively few studies of skin disorders during sleep. Sleep disruption in dermatologic disorders can significantly affect the quality of life and mental health of the patient and in some situations may even lead to exacerbations of the dermatologic condition. Sleep and skin disorders interface at several levels: (1) the role of the skin in normal sleep physiology, such as thermoregulation, core body temperature control, and sleep onset; (2) the effect of endogenous circadian rhythms and peripheral circadian "oscillators" on cutaneous symptoms, such as the natural trough in cortisol levels during the evening in patients with inflammatory dermatoses, which most likely results in increased pruritus during the evening and night; (3) the effect of symptoms such as pruritus, hyperhidrosis, and problems with thermoregulation, on sleep and sleep-related quality of life of the patients and their families; (4) the possible effect of primary sleep disorders, such as insomnia, sleep apnea, sleep deprivation, and circadian rhythm disorders, on dermatologic disorders; for example, central nervous system arousals from sleep in sleep apnea can result in increased sympathetic neural activity and increased inflammation; and (5) comorbidity of some dermatologic disorders with stress and psychiatric disorders, for example, major depressive disorder and attention deficit hyperactivity disorder (ADHD) that are also associated with sleep-related complaints. Sleep loss in atopic dermatitis (AD) is likely involved in the pathogenesis of ADHD-like symptoms in AD. Scratching during sleep, which may be proportional to the overall level of sympathetic nervous activity during the respective stages of sleep, usually occurs most frequently during non-rapid eye movement (NREM) stages 1 and 2 (vs stages 3 and 4 which are the deeper stages of sleep), and in rapid eye movement (REM) sleep, where the severity of scratching is similar to stage 2 sleep. Patient and parental reports of nocturnal itch and scratching in AD typically do not correlate with objective measures of scratching.

Introduction

Sleep is an active process that occupies about one-third of the lives of human beings; however, there are relatively few studies of skin disorders during sleep.[1] Sleep disturbance in dermatologic conditions (eg, as a result of pruritus) can seriously impair the quality of life of the patient and has been associated with serious psychopathology, including increased suicide risk.

Secondly, certain sleep-related pathologies, such as sleep deprivation and sleep apnea, may exacerbate an underlying dermatologic condition. Human sleep is the culmination of two processes: (1) the homeostatic sleep drive, which is determined by the duration of prior wakefulness, and relative sleep debt that the patient may be experiencing, and (2) the circadian system with the central circadian pacemaker located in the suprachiasmatic nucleus of the hypothalamus, which plays a major role in ensuring both consolidated

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nighttime sleep and consolidated daytime wakefulness.[2] It is noteworthy that the pineal gland hormone, melatonin, which is considered to be one of the key indicators of circadian homeostasis, was discovered[3] in 1958 by the group of Yale dermatologist Aaron B. Lerner,[4] that was investigating an earlier finding that pineal extracts from cow brains could lighten the color of tadpoles.

Clinically, sleep and skin disorders interface at several levels:

1. the role of the skin in normal sleep physiology, such as thermoregulation and sleep onset;
2. the effect of endogenous circadian rhythms and peripheral circadian "oscillators" on cutaneous symptoms; for example, the natural trough in cortisol levels during the evening, which is possibly a factor in the observation that most patients with inflammatory dermatoses report increased pruritus during the evening and night;
3. the effect of cutaneous symptoms, such as pruritus, hyperhidrosis, and problems with thermoregulation, on sleep and sleep-related quality of life of the patients and their families: dermatologic disorders most commonly result in insomnia and sleep maintenance disorders, frequent nighttime waking by a child with atopic dermatitis can seriously disrupt the sleep of family members and affect the mental health of the parents, and cutaneous lesions (eg, in infantile eczema) may interfere with the caregiver's ability to caress and hold the child, when being put to sleep;
4. the possible effect of primary sleep disorders, such as insomnia, sleep apnea, sleep deprivation, and circadian rhythm disorders on dermatologic disorders; and
5. the comorbidity of some dermatologic disorders with psychiatric disorders (eg, major depressive disorder and posttraumatic stress disorder) that are also associated with sleep-related complaints.[5]

Psychologic stress is often associated with sleep disturbance and, therefore, sleep difficulties, such as insomnia, may precede a flare-up of the stress reactive dermatoses[6] including acne.[7] These factors are not mutually exclusive and have important implications in the management of dermatology patients.

Normal sleep-wake physiology and the skin

Normal human sleep consists of two states—rapid eye movement (stage R, previously referred to as stage REM and paradoxical sleep) and non-REM (NREM) sleep (stages N1, previously stage 1; N2, previously stage 2; and N3, previously stages 3 and 4 or slow wave sleep)—that alternate cyclically throughout the night.[8] The first episode of REM sleep occurs about 80 to 100 minutes after sleep onset, and the NREM and REM sleep stages cycle through the night, with a period of approximately 90 minutes.

Sleep–wake behavior is typically evaluated with overnight polysomnography and actigraphy. Polysomnography, which involves the simultaneous recording of several physiologic parameters, with a minimum of electroencephalogram, electrooculogram, and submental electromyogram, is used to stage sleep. Depending on the patient's sleep complaints, other physiologic measures may be monitored in a polysomnogram, including respiratory effort and airflow, oximetry, heart rate, and tibialis anterior muscle electromyogram.

In adults, sleep begins in NREM sleep, and the NREM stages N1, N2, and N3 roughly indicate a continuum of depth-of-sleep. Arousal thresholds are generally the lowest in stage N1, which is typically the first stage after sleep onset and are highest in stage N3, the deepest stage of sleep. The characteristic electroencephalogram waveforms in NREM sleep include sleep spindles and K-complexes in stage N2 and high-voltage slow waves in stage N3. NREM sleep is usually associated with minimal mental activity and is a physiologically quiescent stage that is essential for restorative sleep.

The electroencephalogram in REM sleep consists of low-voltage mixed-frequency activity suggestive of electroencephalogram activation that occurs in association with fluctuations in autonomic activity (manifesting as changes in heart rate, respiration, skin conductance, etc.), similar to the waking state, with bursts of rapid eye movements on the electrooculogram and muscle atonia on the electromyogram. REM sleep is associated with dreaming. NREM sleep is dominant during the first third of the night, and REM sleep is dominant during the last third of the night.

The skin and its appendages are well innervated with a dense network of afferent sensory nerves and efferent autonomic nerves.[9] The afferent sensory nerves in the skin convey sensations for touch, pain, itch, temperature, and other physical stimuli. The efferent autonomic, mainly sympathetic nerves, play a role in maintaining cutaneous homeostasis by regulating vasomotor and pilomotor functions and the activity of the apocrine and eccrine sweat glands. Unlike most other organ systems, autonomic nervous system activation of the skin during sleep[10] manifests mainly as signs of sympathetic activation with contraction of the pilomotor smooth muscle and increase in both the thermoregulatory and apocrine aspects of sweat gland activity.[9] This is also associated with changes in skin conductance, which tends to be a reliable index of the sympathetic nervous tone in humans.

Central nervous system (CNS) arousals occur from sleep, spontaneously or secondary to a wide range of pathophysiologic processes, including sleep apnea, pruritus, and pain. Arousal from sleep is associated with increased sympathetic neural activity and may be associated with transient increases in blood pressure, heart rate, muscle, and cutaneous sympathetic nervous activity. A quantitative analysis of sleep stages and CNS arousals provides an index of severity for some sleep disorders and can be used as an objective outcome measure for the efficacy of treatment interventions (eg, in pruritic skin disorders that interfere with sleep).

Although not a replacement for polysomnography, actigraphy[11] is a technology (an accelerometer and memory to record movement data for prolonged periods) that is based on the premise that there is little movement during sleep and increased movement during wakefulness. Actigraphs record limb movement and are usually placed on the wrist, although sometimes leg activity may be recorded. Actigraphy has been used to record scratching during sleep. The actigraphy data, using computer algorithms, are analyzed for activity and inactivity, and wake and sleep states, respectively. Actigraphy is much less expensive than polysomnography, allows recordings of activity and rest in natural environments for days to weeks, and is generally well tolerated. Actigraphy is useful in the evaluation of insomnia, because symptoms tend to vary and may be especially helpful in evaluating insomnia associated with nocturnal scratching in pruritic skin disorders. Actigraphy is also helpful in the evaluation of circadian rhythm disorders.

Circadian rhythms and the skin

Circadian rhythms, which are genetically determined, endogenous timing systems, exhibit oscillations with the period of approximately 24 hours, which closely matches and can be entrained to the daily light/dark cycles. The most commonly used markers of internal biologic time in humans are the circadian rhythms of body temperature and the circadian rhythms of hormones cortisol and melatonin.[12] Light is the primary stimulus that entrains the human circadian system, and nonphotic time cues have a much weaker capacity for resetting circadian rhythms.[12]

Core body temperature and role of the skin in thermoregulation

The suprachiasmatic nucleus plays a role in the timing of a variety of physiologic functions, including the circadian component of thermoregulation of core body temperature (CBT)[13] over a period of approximately 24 hours. The CBT is maintained close to 37°C and has predictable fluctuations during the course of a 24-hour day. The CBT is higher during the daylight hours than during the night hours. The CBT rises in the morning, about the time of dawn, and continues an upward trend until midday, when it plateaus briefly, and then continues its upward trend until the early evening, after which it falls and has a trough in the early hours of the morning. This pattern persists whether an individual is asleep or awake, a day worker or night worker, and is under the control of the circadian timing system. Sleep is most likely to occur on the declining portion of the CBT curve, when the CBT is falling the fastest. The sleep-related fall in CBT is not simply a result of behavioral quiescence during sleep but is also actively regulated by a decrease in metabolic heat production and an increase in heat loss through increased peripheral vasodilatation and sweating.

The skin is important in thermoregulation,[13] defined as the process involved in maintaining the CBT at an optimal level for physiologic functioning. If thermoregulatory function is impaired as a result of a skin disorder and heat is not dissipated as easily through the periphery, sleep onset may be prolonged, and the patient may experience a decrease in restorative slow wave sleep. In general, the latency to sleep onset is the shortest, the sleep is longer and of higher quality (ie, more slow wave sleep) when sleep occurs at a time when the CBT is low and melatonin level is high.

First described by Aschoff[13] in the 1950s, thermoregulation involves a system made up of a "core" or central zone, where the temperature is maintained close to 37°C, and a "shell," where the temperature varies over a much wider range. The "core" temperature is regulated by changes in the temperature of the "shell", which includes distal skin sites such as the skin of the hands, feet, and face. CBT is maintained by both heat loss and heat producing pathways. The cold (temperatures in the range of 20° to 30°C) and warm (temperatures > 30°C) thermoreceptors in the skin detect changes in temperature and change their firing rate, and through ascending neural pathways, reach several brain regions, including the preoptic area of the anterior hypothalamus, which is one of the most important sites for temperature regulation. Temperature regulation occurs by shunting of the blood into arteriovenous anastomoses in the "shell" or the distal skin sites. When the behavioral component of thermoregulation (eg, hydration, manipulation of the environment, etc) is not sufficient, the autonomic response is recruited: heat loss occurs through vasodilation and sweating cools down the "core", whereas under cold stress, thermogenesis is initiated through shivering. In healthy individuals, propensity for sleep increases when the distal skin temperature increases relative to the proximal skin temperature, that is, when the distal-to-proximal gradient (DPG) is greater.

The DPG is not just a marker of sleep onset but is a critical causal step in the process.[14] A thermosuit was used to control skin temperature during nocturnal sleep and showed that an increase of 0.4°C in skin temperature significantly suppressed nocturnal wakefulness ($P < .001$) and shifted sleep to deeper, slow-wave sleep stages ($P < .001$), both in young and elderly subjects.[15] Elderly subjects showed a marked sensitivity, in that the 0.4°C increase in skin temperature (an index of heat dissipation and distal heat loss via the periphery), almost doubled the proportion of slow-wave sleep and decreased the proportion of early morning wakening. If thermoregulatory function is impaired and heat is not dissipated as easily through the periphery, sleep onset and depth of sleep may be adversely affected.

Aging has an adverse effect on peripheral blood flow, which may lead to a reduction in the ability to increase peripheral heat loss, which is required to reduce CBT.[16] Psoriasis[17] has been associated with problems with thermoregulation

and reduced ability to dissipate heat. Problems with thermoregulation and an altered DPG in temperature in psoriasis and other dermatologic conditions may possibly lead to difficulties with sleep initiation and achievement of an optimal level of restorative slow wave sleep.

Peripheral circadian oscillators

In addition to the central circadian pacemaker located in the suprachiasmatic nucleus, the circadian timing system[2] is composed of "peripheral oscillators" in most organs and tissues including the skin.[18,19] The circadian clock, whether located in the suprachiasmatic nucleus or peripherally, is a cellular machine composed of proteins with regulated expression that gives rise to circadian rhythms.[19] Circadian "clock" genes are expressed in human skin cells.[19] The skin receives the greatest exposure to light and shows a high-amplitude circadian rhythm in epidermal cell proliferation. [20] Some earlier studies even suggested that extraocular sites, such as the skin, an organ that receives the greatest exposure to light, may play a central role in the human circadian response to light[19,21]; however, other studies have failed to demonstrate this.[19]

Various skin-related factors show circadian rhythmicity, with one of the most important ones being the stratum corneum barrier of the human skin.[20] Studies have shown circadian rhythmicity in transepidermal water loss, skin surface pH, and skin temperature at most anatomic sites, with skin permeability being higher in the evening and night than the morning.[22] Higher transepidermal water loss in the evening suggests that the epidermal barrier function at this time is not optimal, and transepidermal water loss is associated with higher itch intensity in atopic dermatitis.[23] Skin blood flow rates show circadian rhythmicity, with low cutaneous blood flow during morning hours, the highest values found during the afternoon and early evening, with a second peak during the late evening hours before sleep onset.[20]

These circadian rhythms are maintained during treatment with high-potency and medium-potency corticosteroids in healthy skin.[20] Clinically, this could be an important consideration in the use of moisturizers and emollients during the night[23] and the timing of topical drug application[20,22]; for example, it may be advantageous to use topical corticosteroids during the late evening hours, when there also tends to be a rise in inflammatory activity.[20] The diurnal pattern of pruritus, wherein the threshold for pruritus is lower in the evening before bedtime, most likely reflects complex circadian-mediated factors such as lower cortisol levels, decreased epidermal barrier function, and increased DPG in skin temperature.

Melatonin

Melatonin[3,4] is the most commonly used marker of internal biologic time in humans.[12] Circulating levels of melatonin are normally high during the nighttime hours and low during the daytime. Exposure to light, when endogenous melatonin levels are high, leads to an acute reduction in melatonin synthesis and low circulating melatonin levels. Melatonin is reported to be one of the most evolutionarily conserved hormones and has been implicated in hair growth, melanoma control, and suppression of ultraviolet light–induced damage in human skin and human skin-derived cell lines[24] and wound healing.[25] Melatonin has antimutagenic and oncostatic effects,[26] and several studies have linked night shift work to increased risk of several malignancies, such as breast cancer.[26] In contrast to other malignancies, however, working 10 years or more on rotating night shifts was associated with a 14% decreased risk of skin cancer compared with never working night shifts, and this association was strongest for cutaneous melanoma, where working 10 years or more of rotating night shifts was associated with a 44% decreased risk of melanoma.[26]

Cortisol

The secretion of cortisol, the pituitary hormone that is possibly of the greatest clinical relevance in dermatology, is primarily circadian driven and is maximal in the morning, with a progressive decline over the day, reaching its lowest level in the evening after sleep onset. This natural trough in circulating corticosteroid levels during the evening means that its anti-inflammatory effect is at a minimum during this time, and this may be the basis for the finding that up to 65% of patients with inflammatory dermatoses, including atopic dermatitis, chronic idiopathic urticaria, and psoriasis, report increased pruritus during the night.[23]

Sleep deprivation, immune function, and dermatologic disorders

One of the most important functions of the skin is to generate and maintain the cutaneous permeability barrier, localized in the external stratum corneum, which prevents excessive water loss and prevents entry of foreign substances.[27] One night of sleep deprivation can inhibit recovery (eg, after tape stripping) of skin barrier function in humans.[27] An impairment of skin barrier function is present in chronic skin disorders, such as atopic dermatitis and psoriasis. Impairment of skin barrier function has been shown to exacerbate allergic and irritant contact dermatitis.[27] In addition to decreasing barrier function recovery, sleep deprivation can also increase natural killer cell activity and plasma proinflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α.[27] Interleukin-1β and tumor necrosis factor-α are important in the regulation of NREM sleep. There is an extensive literature on the effect of sleep deprivation on immune function that is beyond the scope of this paper.

Sleep restriction of 25% to 50% of the normal 8-hour sleep time has been associated with an elevation of mediators of inflammation.[28] Small and individual subclinical shifts in basal inflammatory cytokine levels can be associated with the future development of metabolic syndrome, most likely due to autonomic nervous system activation secondary to sleep-deprivation.[28] This may be a factor underlying the development of metabolic syndrome in some dermatologic conditions,[29] such as psoriasis, that interfere with sleep. Rats subjected to total or REM sleep deprivation developed severe ulcerative and hyperkeratotic cutaneous lesions localized to the plantar surfaces of their paws and to their tails.[30]

Histamine

Histamine is the major wake-promoting neurotransmitter in the CNS and plays a central role in CNS arousal.[31,32] The histaminergic neurons display elevated discharge activity during states of increased vigilance and are silent during NREM and REM sleep.[31] In the CNS, histamine H1 receptor activation is a key factor in the control of arousal and the regulation of the sleep–wake cycle; in the periphery, histamine is released by mast cells and is a mediator for pruritus, cutaneous pain, vasodilatation, plasma exudation, and edema formation. The sedation caused by the classical first-generation H1 antihistamines (eg, diphenhydramine) that crossed the blood–brain barrier was one of the first indications that histamine was a wake-promoting substance. Heightened states of arousal, such as in posttraumatic stress disorder and panic disorder, can lead to sleep disturbances and unexplained cutaneous symptoms, including chronic idiopathic urticaria and other pruritic states that are most likely mediated by histamine.

Dermatologic associations of sleep disorders

Primary sleep pathologies can complicate the course of dermatologic disorders or contribute to cutaneous symptoms. The following is an overview of the dermatologic associations of some sleep disorders, as classified by the International Classification of Sleep Disorders, Second Edition.[33]

Insomnia

Insomnia[33] is defined by a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate time and opportunity for sleep and results in some form of daytime impairment. Among adults, insomnia complaints typically include reported difficulties with initiating or maintaining sleep or "nonrestorative" (ie, poor quality) sleep. Insomnia among children is often reported by caretakers and characterized by bedtime resistance, an inability to sleep independently, or both. Insomnia Due to Medical Condition[33] describes the clinical situation where the patient's symptoms meet the criteria for insomnia and the insomnia is associated with a coexisting medical condition that is known to disrupt sleep. A wide range of patients with sleep disturbance due to a dermatologic disorder fall under this category,[1] including patients with pruritus and discomfort due to bullous pemphigoid and Stevens-Johnson syndrome or severe systemic symptoms in erythroderma, to problems with pruritus and thermoregulation[17] in psoriasis and pruritus in atopic dermatitis. In addition to itch, a history of psoriatic arthritis,[34] pain of psoriatic lesions,[34,35] and the effect of psoriasis on overall emotional well-being,[34,36] and not body surface area covered with psoriasis or body mass index, were the most significant predictors of sleep disturbance in psoriasis.

Sleep difficulties and psychiatric comorbidity are common in chronic urticaria; in an internet survey[37] of 321 randomly selected chronic urticaria patients in Germany and France, 48% reported that their sleep disturbances from chronic urticaria remained inadequately addressed. One of the cardinal symptoms of many dermatologic disorders is pruritus that is worse during the night,[1] a factor that also contributes to the sleep disruption in pruritic skin conditions.

In the earlier literature, pruritus associated with nocturnal awakenings was considered to have a medical rather than a psychogenic basis. When psychosomatic factors contribute to the pruritus, sleep disruption due to pruritus usually represents an interaction of the sleep physiologic changes associated with psychiatric comorbidity, such as major depressive disorder with the unique pathophysiology of the primary skin disorder.[36,38] Because many pruritic skin disorders, such as atopic dermatitis, psoriasis, and urticaria, can be associated with significant psychologic morbidity[6] the contribution of the comorbid psychiatric condition to the insomnia or Insomnia Due to Mental Disorder[33] should always be ruled out. Depressive disease, for example, has been shown to enhance pruritus perception in a wide range of common pruritic conditions, such as psoriasis, atopic dermatitis (AD), and chronic idiopathic urticaria,[39] and the sleep disturbance associated with depressive illness can further confound the insomnia due to pruritus in these patients.

In the pediatric population, chronic sleep difficulties in the child can lead to significant stress in the rest of the family and even create dysfunctional family dynamics; for example, in children with AD, the parents may be reluctant to set limits for fear that the stress may trigger a bout of pruritus and scratching, leading to subsequent sleep disruption for both the child and the family. The literature on sleep in dermatologic disorders has tended to focus on sleep in children and adults with AD. A review of the literature[40] indicates that up to 60% of children with AD have disturbed sleep, with an increase in frequency to 83% during exacerbations of the AD. In a study[41] of 300 children with AD aged 6 years or younger, 60% of parents reported that the skin condition affected the sleep of their child; cosleeping because of the skin condition was reported by 30%, and 66% of the families were bothered by the cosleeping. Sleep disturbance, and

cosleeping, which was also most likely a direct index of the sleep disturbance in the child, were directly associated with the severity of AD[41] and the degree to which the parents reported that the AD affected the child and family's mental well being.[41]

Sleep disruption resulting from nighttime scratching has been associated with daytime fatigue, mood disorder, and poor work or school performance.[42] A questionnaire study[43] of 77 children aged 6 to 16 years with atopic eczema and 30 healthy controls revealed that the atopic eczema patients had significantly more sleep problems that were in the clinical range and higher levels of attention deficit hyperactivity disorder and oppositional behavior; whether the daytime behavioral problems were directly related to the eczema or to the effect of eczema on the patients' sleep quality was not clear.

In a German epidemiologic study[44] of more than 13, 000 children aged 3 to 17 years, attention deficit hyperactivity disorder and atopic eczema were strongly related (odds ratio, 2.67;95% confidence interval, 1.03–3.97) in children with sleeping problems but not in children without sleeping problems (odds ratio, 1.24;95% confidence interval, 0.83–1.84). In addition, sleep disruption due to pruritus may contribute to the wide range of psychologic morbidity that is observed in some pruritic skin disorders such as AD.[42] Suicidal ideation in more severe AD may be related to the chronic sleep deprivation due to pruritus.[45]

Studies of insomnia using polysomnography and actigraphy

More than 3 decades ago sleep was studied using overnight polysomnography in 15 patients[46] with the range of pruritic conditions including atopic eczema, dermatitis herpetiformis and psoriasis, and 4 adults with longstanding and severe atopic eczema[47] and it was noted that scratching occurred most frequently[46,47] during NREM stages 1 and 2 (rather that stages 3 and 4 which are the deeper stages of sleep), and in REM sleep, where the severity was similar to stage 2 sleep. The pattern of scratching, which was similar for all the skin disorders studied, seemed to be related to the physiology of the sleep stages rather than the skin disorders themselves.[46] The frequency of scratching during the different sleep stages[47] appeared to be proportional to the relative level of sympathetic nervous system activity normally observed during the respective sleep stages, that is, the progressive decline of sympathetic nervous activity in NREM sleep from stages 1and 2 to slow wave sleep stages 3 and 4, with increased and more variable sympathetic tone during REM sleep.[48]

This was in contrast to the findings of another study,[49] where the sleep stage tended to remain stable for 40 seconds before a bout of scratching, but scratching was followed by a lighter sleep stage, showing that scratching was not the result but the cause of a lighter stage of sleep. This is not supported by the observation that scratching is typically not associated with awakenings from sleep, even though scratching has been reported to fragment sleep (with greater number of stage changes and arousals on the polysomnogram).[50] Patient reports of nocturnal itch and scratching typically do not correlate with objective measures of scratching,[1,42,50,51] and this has been attributed to patients not being fully awakened by the scratching,[50] even though this has not been a consistent finding.[42] In addition, there is an absence of a correlation between parental ratings of restlessness in the child with AD and objective ratings of scratching by actigraphy.[52] Scratching in bed, even in the absence of significant pruritus, can become a conditioned response in some patients.[53]

These earlier findings[46,47] have been supported by most subsequent studies[42,54] of pruritus in dermatologic conditions. Lichen simplex chronicus[54] involves repeated rubbing or scratching, or both, and resultant lichenification that is often associated with nighttime pruritus, scratching, and disruption of sleep. Patients may be unaware of their nighttime scratching behavior,[54] which can in turn lead to impairment in daytime functioning, emotional stress, and scratching as a result of the stress, thereby creating a scratch-sleeplessness-emotional distress-scratch[54] cycle in lichen simplex chronicus that perpetuates the disorder. Polysomnographic evaluation[54] of 15 lichen simplex chronicus patients (aged 37 to 67 years) and 15 healthy controls revealed significantly ($P < .05$) higher percentage of stage 2 sleep, significantly lower percentage of stages 3 and 4 slow wave sleep, and significantly more arousals and awakenings, mainly from NREM sleep, with scratching episodes observed most frequently during stage 2 NREM sleep.

Several other studies have examined nighttime sleep in AD. In a study of 9 children aged 3 to 15 years with AD and a 2-year or longer history of nighttime pruritus, the average frequency of scratching was greatest for stage 1 sleep, followed by stage 2, REM sleep, and stages 3 and 4.[38] The patients had significantly lower percentage of stage 4 sleep and shortened latency to REM sleep, in contrast to age matched controls.[38] Some of these sleep physiologic findings[38] are also present in clinical depression, suggesting that the sleep continuity problems in AD may be partly related to depressive disease and not just nocturnal pruritus and scratching. Twenty adults, aged 18 to 65 years with mild to moderate AD, were studied using patient self-ratings, polysomnography, and actigraphy.[42] The participants spent significantly greater proportion of their time scratching in stages 1 and 2 vs stages 3 and 4 and REM; scratching in REM occurred only with arousal from sleep. All scratching events occurred only during sustained wakefulness or in association with arousals or awakenings from sleep; however, objectively measured scratching did not correlate with the self-assessment itch rating,[42] and patient-rated Dermatology Life Quality Index scores did not correlate with the polysomnographic or actigraphic ratings of sleep efficiency.[42]

Overnight polysomnography of 14 children with AD (mean ± standard deviation age, 6 ± 2 years), which was done

at a time when the AD was in remission, showed that the AD group had significantly ($P < .001$) more arousals and awakenings (24.1 ± 8.1 events per hour) vs age- matched controls with "benign" snoring (15.4 ± 6.2 events per hour); in the AD group, only 15% of the arousals and awakenings were associated with scratching and the rest of the arousals/awakenings were not associated with any identifiable polysomnographic event such as scratching, leg movements or respiration related events.[55] Factors other than scratching contribute to the sleep disturbance in AD patients, a finding that has been noted by other investigators,[38] and this may be related to heightened psychophysiologic reactivity in this patient population.

The literature[42,52,56] suggests that although patient self-report is a poor measure of sleep quality, objective measures such as actigraphy can be a useful tool for measuring scratching and sleep quality in AD. Actigraphic recordings have been shown to be significantly correlated with video-recording[52] measures of sleep, restlessness, and scratching, and also polysomnographic[42] indices of sleep latency, sleep efficiency (an index of wakefulness after sleep onset), and stage 2 sleep (sleep stage when scratching is most likely to occur). Because actigraphic measures have been shown to correlate directly with polysomnographic indices, as well as scratching and disease severity in AD, the use of actigraphy has been suggested as an objective measure of sleep and quality of life in AD patients.[42,57]

Sleep-related breathing disorders

Sleep-related breathing disorders are characterized by disordered respiration during sleep, and snoring is a key symptom.[33] The most common sleep-related breathing disorder is obstructive sleep apnea (OSA), in which there is an obstruction in the airway resulting in continued breathing effort but inadequate ventilation.[33] Sleep-related breathing disorders, such as OSA, are associated with frequent arousals from sleep, which in turn results in sympathetic activation. The sympathetic activation in OSA can in turn alter the homeostasis of the immune neuroendocrine network[58,59] in the skin, and this can[58] precipitate inflammatory skin disorders, such as psoriasis, in genetically predisposed individuals by the secretion of proinflammatory neuropeptides.

In a polysomnographic study[58] of 25 adults with psoriasis and 19 age- and sex-matched patients with chronic bronchitis, a condition known to be associated with OSA, OSA (defined as an apnea index of >10 per hour of sleep in this study, which is a conservative definition of OSA compared with standard criteria[33]) was observed in 36% of psoriasis patients vs 32% of patients with chronic bronchitis ($P = .03$). The authors[58] also made a preliminary observation that successful treatment of OSA with nasal continuous positive airway pressure (CPAP) may improve psoriasis patients' response to antipsoriatic therapies and prolong the patients' disease-free period.

Sleep-related sweating, measured by electrodermal activity during sleep, can be a feature of OSA[60] that is most likely due to the sympathetic activation caused by sleep-related breathing disorder. Patients with higher electrodermal activity indices had higher systolic blood pressure during the evening and morning, and a lower percentage of REM sleep.[60] Treatment of the OSA with 3 months of CPAP therapy was associated with a lower electrodermal activity index, lower blood pressure, and an increase in the percentage of REM sleep.[60] Alternately, snoring and OSA in children with AD[61] can be an indication of allergic rhinitis and asthma, which are typically comorbid with AD, and predispose the child to develop OSA. Hyperpigmentation and lichenification of the forehead skin were observed in a morbidly obese patient with severe OSA who could only sleep by sitting upright and leaning his head against the wall.[62]

Narcolepsy

Narcolepsy is a hypersomnia of central origin, associated with excessive sleep propensity during the day that has been associated with hypocretin deficiency. Patients with narcolepsy[63,64] have alterations of daytime skin temperature and a DPG in skin temperature that is higher than that achieved in healthy controls when asleep, a situation that is consistent with the excessive daytime sleepiness in these patients. A potential association between alopecia areata and narcolepsy[65] has been suggested based on five case studies, with a discussion of possible common autoimmune factors in both disorders.

Circadian rhythm sleep disorders

Circadian rhythm sleep disorders[33] can result from a misalignment between the timing of the individual's circadian rhythm of sleep propensity and the 24-hour social and physical environments. Some common clinical situations include shift work and jet lag. Cortisol secretion has a diurnal pattern: it is low during the early hours of the morning and high at about 8:00 AM. This diurnal pattern of cortisol secretion, which is primarily under the control of the circadian system, may continue for 21 days under conditions of constant light. If the sleep–wake rhythm is shifted from the typical 24-hour cycle, it can take 1 to 2 weeks for cortisol secretion to move to the new rhythm. Patients with frequently changing shift work may experience a flare-up of their inflammatory dermatosis; for example, if they are awake at a time when their cortisol secretion is low. Circadian rhythm sleep disorders can potentially lead to problems with thermoregulation and stratum corneum barrier function integrity, which are also under circadian control.

Parasomnias

Parasomnias (eg, sleepwalking, night terrors) are typically disorders of arousal from sleep that manifest as abnormal

sleep-related movements, behaviors, dreaming, and autonomic nervous system functioning.[33] In a questionnaire study of 57 AD patients and age-matched controls, AD patients reported significantly more parasomnias, and the frequency of parasomnias was directly related to disease severity in AD.[53] This finding was attributed to "sensory hypersensitivity" and "hyper-arousability" in AD.[53] A study of 116 patients with vitiligo and 52 patients with other dermatologic disorders that are not generally associated with psychosomatic pathophysiology revealed that vitiligo patients had a significantly higher frequency of parasomnias in childhood and adolescence before the onset of their vitiligo.[66] This was attributed to possible common neuropathologic factors underlying both disorders. Three case studies of nocturnal scratching, including sole scratching of the perianal area, manifesting as a chronic NREM parasomnia in the absence of a primary dermatologic disorder, have been described.[67] A study of 34 participants with nocturnal motor agitation or behaviors observed that paroxysmal arousals from sleep with motor behaviors such as scratching can be a manifestation of nocturnal frontal lobe epilepsy.[68]

Restless legs syndrome

Restless legs syndrome is a sensorimotor disorder associated with a nearly irresistible urge to move the legs, which is worse during the evening and which may be accompanied by an unpleasant paresthesia deep within the leg.[33] The paresthesias may be misdiagnosed as skin irritation[69] or some other primary skin problem. In some definitions[70] of restless legs syndrome, also referred to as Ekbom syndrome, dermatologic and sleep disorders may overlap. Ekbom syndrome has also been referred to as a "parasitosis delirium," where patients may have delusions of parasitosis.[70]

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