Nocturnal eczema: Review of sleep and circadian rhythms in children with atopic dermatitis and future research directions

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Children with atopic dermatitis (AD) experience significant sleep disruption, and clinically, the disease is noted to worsen in a circadian manner at night. Epidemiologic findings highlight many negative consequences of AD, such as impaired linear growth, which is uniquely related to disturbed sleep. Clinical guidelines currently recommend assessing sleep in patients with AD as a crucial parameter of disease control with appropriate treatment. In this review we describe our current understanding of the roles of sleep cycles and circadian rhythms in the nighttime exacerbation of AD (nocturnal eczema). We present a schematic to explain the mechanism of nocturnal eczema. Treatment options for sleep disturbance and future directions for research are discussed in the context of AD. (J Allergy Clin Immunol 2015;136:1170-7.)

Key words: *Atopic dermatitis, eczema, sleep, sleep disturbance, circadian rhythms*

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Abbreviations used
AD: Atopic dermatitis
BMAL: Brain and muscle ARNT-like
CLOCK: Circadian locomotor output cycles kaput
NREM: Nonrapid eye movement
REM: Rapid eye movement
TEWL: Transepidermal water loss
WASO: Wake After Sleep Onset

Sleep plays an important role in promoting physical and mental health. Sleep deprivation has been shown to alter immune function.[1] Patients with chronic disease are susceptible to sleep disruption caused by poor illness control, illness-related symptoms at night, and medications used as principal treatments.[2] Atopic dermatitis (AD; also called eczema) is a chronic inflammatory skin disorder affecting 10% to 20% of US children.[3] AD is characterized by intense nocturnal pruritus,[4] which can severely affect sleep continuity, sleep quality, and quality of life. Sixty percent of children with AD experience sleep disturbance caused by their disease, with 83% reporting sleep disturbance during exacerbations.[5-8] In fact, short stature has been described in children with AD only when associated with insufficient sleep.[9]

Given the nocturnal pattern of eczema flares, abnormalities in circadian rhythms (24-hour cycles) or rhythmic secretion of biological factors (eg, cortisol secretion) might underlie the diurnal pattern of itch and flares. Diurnal variation in skin physiology is complex[10,11] and includes both peripheral circadian rhythms (skin and leukocyte-derived oscillations) and central circadian rhythms (directed by pineal gland–derived melatonin and cortisol).[12,13] Circadian variation in the expression of pruritogenic inflammatory cytokines,[14] such as IL-2 and the pruritus-specific T_H2 cytokine IL-31,[15,16] might drive nocturnal AD flares. Nighttime factors, such as cortisol nadir, increased skin temperature and poor barrier function (leading to increased transepidermal water loss [TEWL]),[17] neuropeptide-induced sensitivity,[18] susceptibility to infections,[19,20] and itch exacerbation by bacterial products, such as staphylococcal superantigens, irritants, and allergens, can all promote the hallmark of inflammatory T_H1, T_H2, and T_H22 cellular infiltrate[21] in patients with AD, homing to skin secondary to diurnally mediated chemokine gradients.[22]

In this review we describe our current understanding of the roles of sleep cycles and circadian rhythms in the nighttime exacerbation of AD (nocturnal eczema, Fig 1). Treatment options for sleep disturbances and future directions for research are discussed in the context of AD.

STAGES OF SLEEP IN CHILDREN

By around 3 months of age, 24-hour sleep architecture begins to become structurally more predictable and reproducible. Sleep is defined polysomnographically by 4 stages.[23-25] A typical night of sleep involves multiple cycles through stages N1-N3 (nonrapid eye movement [NREM]) and rapid eye movement (REM) sleep. During the first year of life, NREM and REM sleep are equally

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Disclosure of potential conflict of interest: P. C. Zee owns stock in Teva; has consultant arrangements with Merck, Jazz, Vanda, Philips Respironics, and Pernix; and has received grants from Jazz. F. W. Turek has consultant arrangements with PatientsLikeMe and has received grants from the Department of Defense, the Office of Naval Research, the National Institutes of Health, NASA, Merck, and Vanda Pharmaceuticals. S. H. Sheldon has consultant arrangements with Dymedix and has received payment for lectures from Cadwell Diagnostics. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 6, 2015; revised August 7, 2015; accepted for publication August 11, 2015.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.08.028

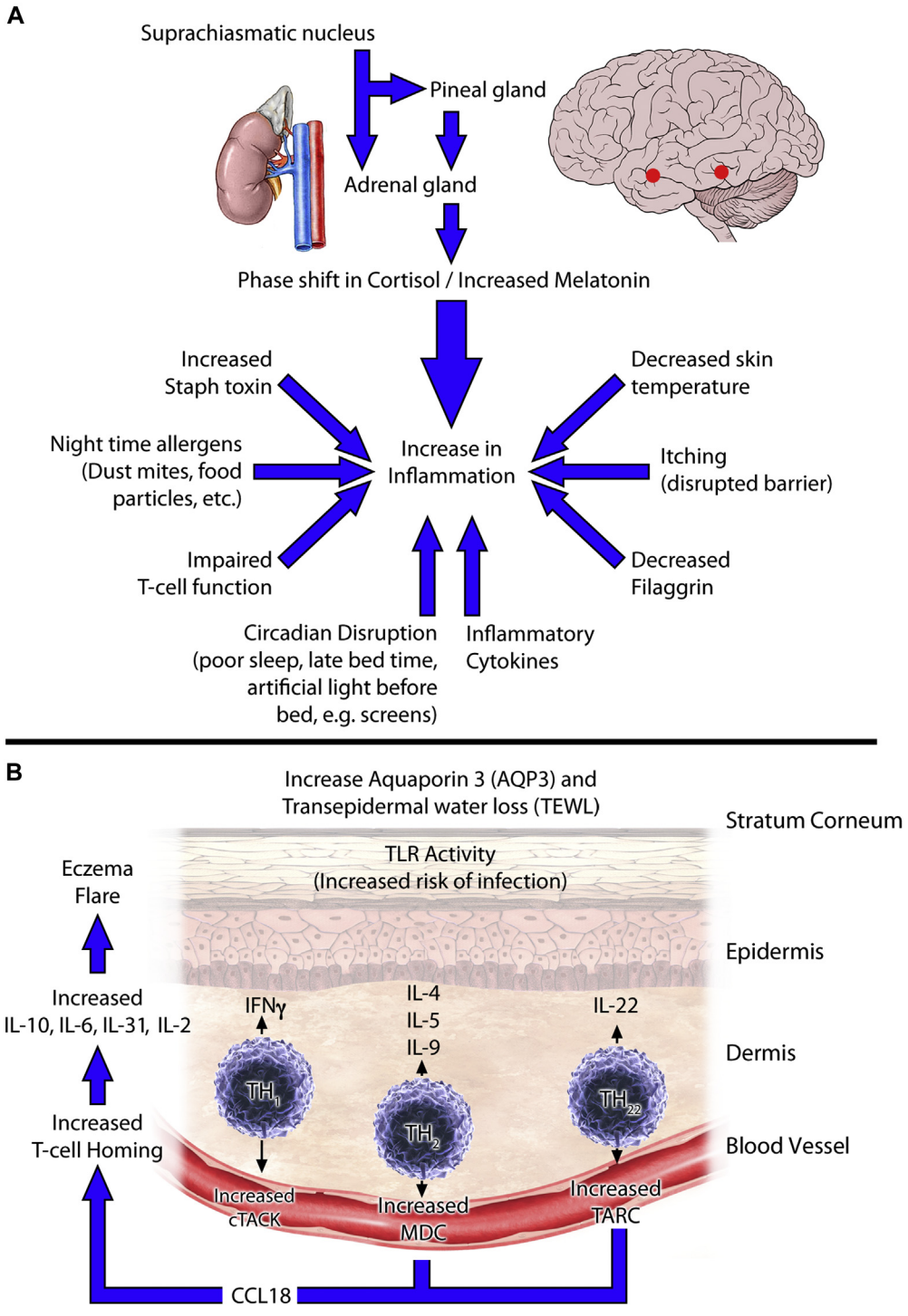

FIG 1. Schematic of the mechanism in nocturnal eczema exacerbations. **A,** Central circadian rhythms are directed by the suprachiasmatic nucleus, which stimulates cortisol release by the adrenal glands and melatonin release by the pituitary gland. In patients with eczema, melatonin levels can be increased and cortisol rhythms shifted from normal timing of production, resulting in increased systemic inflammation. Other nocturnal stimuli (local and systemic) that upregulate inflammation are drawn with *arrows*, including the vicious itch/scratch cycle that results from inflammation and leads to further barrier impairment. **B,** Poor barrier function is made worse at night by increased TEWL, increased aquaporin-3 *[AQP3]* expression, increased T-cell activation, and upregulated Toll-like receptor *(TLR)* expression. These feed back to increase systemic and skin-directed T_H1, T_H2, and T_H22 cytokines. Published literature suggests that these cytokines and chemokines (thymus and activation-regulated chemokine *[TARC]*, macrophage-derived chemokine *[MDC]*, cutaneous T cell–attracting chemokine *[cTACK]*, and CCL18 [also known as pulmonary and activation-regulated chemokine]) are upregulated at night in patients with eczema, stimulate T-cell homing, and increase further production of inflammatory cytokines, some of which directly disrupt sleep (IL-6) or exacerbate pruritus (IL-31), resulting in eczema flare.