

## Review Article

# Atopic Dermatitis beyond the Skin: The Impact on Children's Sleep

Larissa Toledo de Lima Duarte Souza<sup>1</sup> and Juliany Estefan<sup>2\*</sup><sup>1</sup>Dermatologia, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil<sup>2</sup>Dermatologia Pediátrica, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil**\*Corresponding author**

Juliany Estefan, Dermatologia Pediátrica, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil

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**Abstract**

Atopic Dermatitis (AD) is an inflammatory multifactorial disease with genetic, environmental and immunological characteristics. It affects approximately 15% to 30% of children, 1% to 3% of adults, and its prevalence has been increasing. Currently, it is subject of several clinical researchers and new therapies possibilities.

Sleep disorders is prevalent among individuals with AD, resulting in a negative impact of life quality, compromised academic and occupational performance, behavioral alterations and increased stress levels. The literature suggests that AD is associated with sleep disorders in children from 47% to 80% of the cases and from 33% to 90% in adults.

This is a descriptive study, characterized as a narrative literature review. The research was based on of studies published in English and Portuguese between January 2013 and August 2023, which are available in electronic media from various databases, such as PubMed, Scientific Electronic Library Online and Latin American and Caribbean Literature on Health Sciences. The aim of this review is to describe the relationship between atopic dermatitis and sleep disorders, in order to contribute to a better understanding and clinical management of atopic dermatitis.

AD can affect the lives of individuals to varying degrees, as well as their families. Sleep assessment, multidisciplinary monitoring and appropriate treatment are crucial to improving the general wellbeing of individuals affected by AD.

**Keywords**

- Atopic Dermatitis
- Sleep
- Psychological Stress
- Insomnia
- Pruritus

**INTRODUCTION**

Atopic Dermatitis (AD), or atopic eczema, is a chronic inflammatory skin condition characterized by a combination of genetic, environmental, and immunological factors [1]. This multifactorial disorder presents three distinct clinical forms: acute, subacute, and chronic. It is marked by xerosis, cutaneous lesions, persistent pruritus, and a cyclical nature, involving periods of remission and relapse [2].

Individuals diagnosed with AD often have a family or personal history of atopy [3]. Various factors contribute to the initiation and progression of AD, encompassing congenital skin barrier abnormalities, allergies, microbial colonization, and autoimmunity [4]. AD may also coincide with other allergic manifestations like rhinitis, asthma, and food allergies due to compromised skin barrier function, inflammation, and concurrent epicutaneous allergic sensitization, which promote the development of allergic comorbidities [5].

Sleep disorders are common in patients with AD and it is one of the factors that can most impact the patient quality of life. Sleep disturbance may affect up to 83% of children during

eczema flare-ups. However, studies aimed the clinical treatment of sleep disorders are limited [6].

The primary therapeutic approaches for AD involve the restoration and maintenance of the skin barrier, reduction of lesions and identification and elimination of triggering and/or exacerbating factors [7].

**MATERIALS AND METHODS**

A narrative literature review was conducted, with a literature search of studies published between January 2013 and August 2023 that are available in electronic media from several databases, such as PubMed, Scientific Electronic Library Online and Latin American and Caribbean Literature on Health Sciences. Health Sciences Descriptors "atopic dermatitis" and "sleep" were used.

**Justification**

This literature review is important since AD is a condition that is frequent observed, especially in children, which can compromise patient's lives in different degrees and in many spheres: physical, emotional, social and economic. Early diagnosis and treatment are important in addition to a multidisciplinary monitoring to improve life quality.

## LITERATURE REVIEW

AD exhibit a global distribution, affecting approximately 15% to 30% of children, with its prevalence continually rising [2]. The prevalence of AD shows variability across different countries; a study conducted in Brazil estimate an approximate 8% national prevalence [8]. A notably lower prevalence was observed in rural areas in contrast to densely populated urban areas. Moreover, a higher prevalence of AD is associated with families possessing higher socioeconomic status and fewer household members [9-11].

AD tends to manifest predominantly in infants between 3 and 6 months age. Around 60% of patients develop the condition within their first year of life and approximately 90% before reaching 5 years old [12]. In most cases, ranging from 70% to 90%, the condition spontaneously resolves by adulthood [13]. Children who develop AD during their early years have an increased risk of experiencing persistent and more severe manifestations throughout childhood, along with an increased prevalence of atopic comorbidities such as food allergies, asthma, and allergic rhinitis [14]. Despite the absence of a definitive cure, the condition can be effectively managed through treatments and the implementation of preventive skin care measures [15].

AD is a multifactorial disease with a not yet fully elucidated etiology [1], linked to alterations in the skin barrier [16]. AD is characterized by immune system deregulation, primarily marked by cytokine production orchestrated by Th2 helper T cells, yet also encompassing Th1 response [17]. During the acute phase, the Th2 response, driven by IL-4, 5, and 13 predominates. These cytokines are related to the inflammatory phase, with high expression in the regulation of adhesion molecules in endothelial cells and increased eosinophil survival [18,19]. During the chronic phase of AD, a Th1 response takes precedence, marked by elevated levels of Interferon Gamma (INF- $\gamma$ ), IL-2, IL-5, IL-12, IL-18, and Granulocyte-Macrophage Stimulating factor (GM-CSF). These immune factors contribute to the remodelling of the cellular response and their persistence characterizes the chronic manifestation of the condition [20]. As consequence of compromised skin barrier integrity is an increase in Transepidermal Water Loss (TEWL) [16].

Another potential contributor to the onset or exacerbation of AD is the involvement of infectious agents. Patients with AD are at greater risk of developing infection due to damage to the skin barrier, which may be one of the worsening factors of AD [21].

The diagnosis of AD is primarily clinical, relying on the identification of signs and symptoms. These are established based on primary and secondary criteria outlined by Hanifin and Hajka (1980). Histopathological findings lack specificity, and no singular laboratory marker exists [22].

Primary criteria include: skin itching, chronic dermatitis, personal history of atopy, family history of atopy and typical location of the lesions. Secondary criteria include: tendency to skin infections, paleness or facial erythema, anterior neck folds,

alopecia areata, keratoconus, nipple eczema, xerosis, ichthyosis vulgaris, increased total IgE, infraorbital darkening, Dennie Morgan lines, keratosis pilaris, ptyriasis alba, ocular pruritus, cheilitis, palmar hyperlinearity and Hertoghe's sign. According to Hanifin and Rajka (1980), diagnosis entails the presence of at least three of the four major criteria (pruritus; characteristic morphology and distribution; chronic and recurrent course; personal or family history of atopy), alongside three minor criteria.

Skin lesions associated with AD are typified by being pruritic, enduring and cyclical, marked by alternating periods of improvement and recurrence. Clinical manifestations of AD vary according to the age group and can be localized or disseminated. In infants up to six months old, erythematous lesions, vesicles and crust formation typically occur, primarily on the face and extensor surfaces. From two years old, lesions tend to emerge on the flexor surfaces and gradually evolve into lichenified areas. Pruritus is a consistent hallmark throughout all stages, frequently intensifying during night time hours. Xerosis is a distinctive feature of AD, evident in both affected and unaffected skin [23]. The prognosis is mainly determined by the severity [24].

It is extremely important to accurately assess the extent, intensity and severity of AD, it helps in assessing the therapeutic response [22]. Severity criteria were established for follow-up, which assess parameters of extension, intensity of lesions and subjective symptoms, such as pruritus and sleepiness. Among the severity scoring of atopic dermatitis, the SCORAD index is one of the more used. The SCORAD has a maximum score of 103, with values below 25 classified as mild clinical cases; between 25 and 50 moderate and greater than 50 considered severe cases.

Sleep deficiency in children with AD is associated with risk of short stature, metabolic syndrome, mental illness, neurocognitive dysfunction, psychiatric comorbidities such as anxiety, stress, depression, Attention Deficit Hyperactivity Disorder (ADHD), worse school performance, behavioral and mood dysfunction. Sleep disorders and mood changes can also be observed in family members [25-28].

Chang, et al 2014, demonstrated that children with AD have the following sleep disorders: significant reduction in efficiency, longer latency to sleep onset, greater fragmentation, and less non-rapid eye movement sleep compared to individuals healthy. Furthermore, sleep disturbances in children with AD have been associated with scratching and greater severity of dermatitis [25].

In a cohort of children from 6 to 17 years old with moderate to severe AD, around 60% of them experienced altered sleep patterns. However, the underlying mechanisms of sleep disturbances in children with AD remain unclear and there is currently no consensus on the optimal approach to addressing the issues. Studies have suggested that the decrease in melatonin secretion may be involved in the sleep disorder due to its effects on sleep, immunomodulation and as an antioxidant [25,26,29,30].

Cohort study conducted by Ramirez, et al in the United Kingdom evaluated 13,988 children, revealing that AD is correlated with the worsening of sleep quality throughout childhood, although not associated with a reduction in sleep duration. This negative impact on sleep was more prevalent in the severe cases when accompanied by symptoms of rhinitis or asthma. However, the chance of having sleep disturbances remained considerably high even among children who had a mild form of AD and no clinical activity [31].

A study carried out in the United States evaluated the association between eczema in adults and sleep disorders and its impact on general health and the use of health care. Eczema was associated with greater odds of fatigue, daytime loss and insomnia [32]. Furthermore, restless legs syndrome was also more prevalent in patients with AD, although the underlying mechanism of this association remains unclear [33].

Ramirez, et al find that between 26.7% and 49.5% of children with AD experience regular nightmares [31]. The relationship between parasomnias and AD needs further studies to be elucidated, but it is important to note that children with chronic nightmares have more emotional symptoms, hyperactivity, conduct problems and social difficulties compared to those without nightmares or with transient nightmares [34].

A prospective case-crossover study in 10 children with moderate-severe AD assessed using SCORAD and monitored by actigraphy during 14 days, demonstrated that sleep duration was decreased in all subjects and awakenings were increased in 90%. The researchers concluded that children with moderate or severe AD have sleep quality abnormalities and improvement in AD severity upon intensified AD treatment was associated with improved parental perception of sleep loss, but not of objective sleep quality assessed by actigraphy [35].

## DISCUSSION

Sleep disturbances are very common in patients with AD and it is one of the biggest factors that can impact quality of life. Besides, childhood sleep loss influences later development. Despite this, studies aimed at the clinical treatment of these sleep problems are limited. Presently, there is no consensus or available guidelines on how best manage sleep problems in these patients. The disease control is essential to improve sleep, but in some cases some treatments may be necessary to reduce itching at night [36,37]. Regarding the symptoms of AD, sleep disturbance is one of the most observed and also one of the criteria for evaluating the severity of the disease. It has been reported that the main trigger for sleep disturbances is the vicious cycle of itching and scratching however, the literature suggests that this may only partially explain sleep problems [35].

The relationship between sleep and AD is bidirectional and can generate a cycle in the disease. The improvement of skin lesions is important for the consequent improvement of sleep, and with sleep improvement can also be observed an improvement in AD. Some authors suggest that sleep disorders can be seen as

comorbidity in AD and should be evaluated and treated in the same way as it is done for the control of skin lesions [37]. The incidence of sleep disorders reaches roughly 60% of patients with AD [26], may lead to harmful effects on neurocognitive functions, behavior pattern and mood [26]. One of the observed effects is the sleep interruption in children diagnosed with AD as well as in their parents, ranging from mild to profound insomnia. Studies showed that parents of children with AD have difficulties falling asleep and increased night awakenings related to their child condition, which can lead to physical and mental exhaustion, mood swings, loss of concentration and lower performance at work [38].

In general, as the severity of AD worsens, the incidence and intensity of pruritus and sleep disturbances also increase [26]. During periods of AD exacerbation, the prevalence of sleep disorders rises from 60% to 83% [6]. The worsening in the severity of the condition assessed by SCORAD, showed an association with sleeps worsening, night awakenings and marked daytime sleepiness ( $P < 0,0001$ ) [39,40]. The sleep disorders most frequently reported in individuals with AD, children or adults, include: difficulty in initiating sleep, recurrent episodes of nocturnal awakenings and daytime sleepiness, greater number of transitions between sleep phases, resistance to awakening by morning and feeling tired and irritable during the day [41-44].

Various techniques have been employed to investigate subtypes and severity of sleep impairment in AD, as actigraphy, polysomnography, electroencephalography and questionnaires [28]. Polysomnography is the gold standard assessment for sleep, but it is little used to assess sleep in children with AD due to the inconvenience of performing at night and the placement of multiple patches that can also result in more skin damage in the child who already has areas of eczema [37]. Chang, et al demonstrated through actigraphy and polysomnography that children with AD have reduced sleep efficiency, takes longer time to sleep, have greater fragmentation and less non-Rapid Eye Movements (non-REM) compared to healthy individuals [30].

The literature describes that children with AD may present sleep-loss related disturbances as well as unusual behavior disturbances, such as increased movement linked to restlessness, limb movement, scratching, sleep disorder breathing as obstructive sleep apnea or snoring, nocturnal enuresis, hyperhidrosis and nightmares [28]. A study from Singapore shows that snoring was related to AD in preschool and school children [45]. Another study conducted in Taiwan shows that patients with Obstructive Sleep Apnea (OSA), especially young men and children, were more likely to have AD [46]. It is hypothesized that the link between AD and OSA may be related to shared pathways of oxidative stress and systemic inflammation, in addition to an increased sympathetic tone and sleep fragmentation that may contribute to upper airway instability [47,48].

Study of Camfferman, et al evaluated using the Sleep Disorders Scale for Children that a higher percentage of children with eczema had hydrosis during sleep compared to the

control group. Individuals with AD may suffer from itch when exposed to heat or psychological stresses, which are also known perspiration stimuli and some mechanisms of sweat-induced itch have been described [6,49]. Tsai, et al identified that children with atopic dermatitis were significantly more likely to have nocturnal enuresis compared to controls. The pathophysiological connection between AD and nocturnal enuresis is still unknown. One hypothesis is that an intense activation of the parasympathetic nervous system, occurring after repeated allergic reactions, may affect the bladder, resulting in detrusor muscle instability and overactive bladder [1,39,50].

The pathophysiology of sleep disorders in children with AD remains largely unknown. Factors such as the circadian rhythm of cytokines, lower melatonin function, immune system functioning, skin physiology and environmental influences may be involved [1,39]. Bawany, et al proposes possible mechanisms between sleep disorders and AD. First, stress from AD can trigger acute insomnia, which becomes chronic over time. Scratching at night interferes with sleep and generates behaviors that perpetuate insomnia. In addition, those with insomnia may ruminate about stresses and itching in bed, adopting inappropriate practices, which disturbs the sleep rhythm and may persist even after AD improves [39]. Children with AD in remission still had more awakenings per hour than healthy controls, suggesting the influence of persistent behaviors. Pruritus, which is one of the main factors that decrease the life quality of individuals with AD, is often worse at night, leading to scratching and consequently disturbing sleep. While healthy people have little itching during sleep, patients with AD can spend up to 14.3% of their sleep time scratching themselves, causing sleep fragmentation and reduced sleep efficiency. The cycle of itching and scratching can cause tissue damage and release inflammatory and itchy substances, further intensifying sleep problems [51-53].

Several factors contribute to this relationship, such as eosinophil granular proteins and nerve growth factors that result in sensory hypersensitivity [54]. In addition, circadian variations in skin blood flow, water loss through the epidermis and cortisol levels favor nocturnal itching. Some studies have found conflicting associations between substance P and cytokines (such as IL-31) with subjective sleep loss and disease severity, but not directly with pruritus [39,55,56]. Another perspective on the relationship between sleep disturbances in Attention Disorder focuses on circadian variations of cytokines and melatonin. Some cytokines promote sleep at night (IL-1 $\beta$ , IL-2, IL-6, TNF- $\alpha$ , and IFN- $\gamma$ ), while others stimulate wakefulness after waking up (IL-4, IL-10, and IL-13) [57,58]. AD is believed to cause a disruption in these circadian cytokine patterns. The presence of IL-6 in the morning is linked to a reduction in sleep quality in patients [57]. In addition, melatonin, which regulates sleep and circadian rhythm, also plays an immunomodulatory and antioxidant role. Studies indicate that most AD patients do not experience the normal night-time melatonin peak, which are associated with more efficient and less fragmented [30,39,59].

## CONCLUSION

AD is a chronic and relapsing inflammatory disease, which

can impact the lives of individuals in different ways. The physical, emotional, social, work, academic and economic spheres can be negatively impacted. In general, the severity of AD compromises proportionally the sleep, the psychological profile and the life quality of patients and their families. Regardless of the severity of the condition, all individuals must be fully evaluated. Pruritus is the main symptom observed in the disease being generally more difficult to control at night, resulting in frequent nocturnal awakenings. In addition, during the night awareness of itching can also be intensified, resulting in more friction and abrasions, which can be a factor that worsens school performance and the clinical presentation of AD. The consequences of sleep loss are daytime fatigue, headaches, neurocognitive and mood disorders, behavioral problems and reduced school and professional performance. Therefore, it is extremely important to improve sleep quality to control the disease and improve quality of life. However, studies designed to guide the clinical treatment of these sleep problems are still limited.

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