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Sleep Patterns and Development of Children with Atopic Dermatitis

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Keywords
Atopic dermatitis · Child development · Sleep problems

Abstract
Introduction: Atopic dermatitis (AD) is a chronic inflammatory disease that begins in early childhood. Sleep problems have increased in children with AD. The aim of this study was to evaluate sleep patterns and the development of children with AD at an early age. ***Methods:*** This is a cross-sectional study consisting of a total of 80 children aged 0–36 months with AD. Patients were evaluated by the Brief Infant Sleep Questionnaire and International Guide for Monitoring Child Development. ***Results:*** The median age (IQR) of the patients was 6 (4.25–9) months, 63.7% of them were male and 50% of them had sleep problems. Male sex (OR: 3.78, $p = 0.024$, 95% CI, 0.083–0.837), patients with AD who were in the first 3 months after diagnosis (OR: 3.56; 95% CI, 1.220–10.43, $p = 0.020$), and moderate-severe AD (OR: 5.09; 95% CI, 1.649–15.748, $p = 0.005$) were determined as risk factors for sleep problems. In all, 12.5% of the patients needed support for one or more developmental areas (gross motor skills, expressive language and communication, receptive language, fine motor skills, relationship, and play). Developmental delay was higher in patients with sleep problems ($p = 0.037$). Multiple siblings (OR: 14.381; 95% CI, 1.557–132.871, $p = 0.019$) and the presence of sleep problems (OR: 8.011; 95% CI, 1.764–36.387, $p = 0.024$) were found to be risk factors for developmental delay. ***Conclusion:*** Boys with moderate-severe AD within the first 3 months of diagnosis were at increased risk for sleep problems. Children with AD who have multiple siblings and sleep problems should be evaluated for developmental delay and monitored closely.

Introduction

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease that usually begins in early childhood [1]. The prevalence of AD in children is 15–20%, and its incidence in developed countries has increased by 2–3 times in recent years [2]. In the first year of life, the prevalence of AD was 4.3% in a cohort study conducted in Turkey [3]. The main clinical features of AD are skin re-

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activity and intense itching at night [1]. The frequency of sleep problems has increased in children with AD because of itching and scratching, which interfere with falling asleep and sleep continuity [4]. Delay in sleep onset, frequent night waking, and decrease in sleep duration are the most frequently reported sleep problems in children with AD [5, 6]. Sleeping is necessary for the cognitive and behavioural development of the child [7, 8]. This study aimed to evaluate sleep patterns and the development of children with AD at an early age and to determine the factors affecting sleep patterns. To the best of our knowledge, this is the first study evaluating both development and sleep patterns together in patients aged 0–36 months with AD.

Materials and Methods

This is a cross-sectional study consisting of a total of 80 children with AD. The statistical power calculation for the sample was performed using the NCSS-PASS programme. According to the power calculation programme, we included 80 children in the study to assess sensitivity and specificity with a power of 0.8 and alpha of 0.05. Patients were followed up in the Pediatric Allergy and Immunology Department at the Health Sciences University, Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Ankara, Turkey, between February 2018 and February 2019. The ethical approval for this study was received from the Ankara Child Health and Diseases Hematology Oncology Training and Research HospitalEthical Committee.

Patients

The study population was composed of paediatric patients aged 0–36 months. The majority of the patients we followed in the Pediatric Allergy and Immunology Department constitute the preschool age group. The sleep questionnaire we used has validity in children aged 0–36 months, and this is why the sample size was limited to this age group. Parents of the patients followed at the Pediatric Allergy and Immunology Department for AD were invited to participate in the study. A total of 80 patients whose parents agreed to participate in the study and met the inclusion criteria were included in the study. The flow chart of the patients is shown in Figure 1.

Patients aged 0–36 months diagnosed with AD according to the criteria set forth by Hannifin and Rajka [9] were included in the study. Patients were classified according to the SCORing Atopic Dermatitis (SCORAD) index, which is one of the most commonly used tools to assess the severity of AD. Scores below 25 are classified as mild, scores 25–50 are classified as moderate, and scores over 50 are classified as severe AD [10]. Patients with chronic diseases other than AD, such as neurometabolic disease, were excluded from the study.

The case report form containing the sociodemographic characteristics and clinical information of the patients whose parents agreed to participate in the study was recorded. The sleeping pattern of the participants was evaluated with the Turkish version of the Brief Infant Sleep Questionnaire (BISQ), and the developmental characteristics of the patients were evaluated with the International Guide for Monitoring Child Development (GMCD) by a single investigator.

Brief Infant Sleep Questionnaire

The BISQ is a sleep questionnaire aimed to evaluate the infant's average sleep patterns. It is a highly validated measure for children up to 3 years old. The parents are instructed to define their children's regular sleep patterns. The derived measures are sleep onset time, nocturnal sleep duration, daytime sleep duration, number of night wakings, and sleep latency (the reported length of time it takes the child to fall asleep). The BISQ defines poor sleepers according to 1 or more of 3 measures: (1) night waking >3 times, (2) nocturnal wakefulness >1 h, or (3) total sleep time is <9 h [11]. The validity and reliability for the Turkish version were performed by Boran et al. [12]. Author permission was obtained to use the questionnaire.

International Guide for Monitoring Child Development

The GMCD is a comprehensive package that comprises three components: monitoring, supporting early childhood development, and early intervention [13]. It is internationally standardized. The sensitivity and specificity of the GMCD were found to be 0.87 (0.77–0.94) and 0.72 (0.70–0.74), respectively [14]. The GMCD provides a detailed developmental assessment in seven different areas: expressive language and communication, receptive language, fine and gross motor skills, relationship (social-emotional), play (social-emotional and cognitive), and self-help skills (for children older than 12 months). Each developmental area is evaluated separately. The GMCD is a 10-min interview that asks structured, open-ended questions about each domain. The GMCD has a table format, with the seven domains arranged in rows and the columns indicating the age intervals. Milestones in each domain are fitted into appropriate age intervals, so the lower and upper ages of an interval would approximate the 85 and 97th percentiles. These percentiles used in the development of screening instruments approximate 1 and 2 standard deviations (SDs) beyond the mean. Typically, developing children attain all milestones on the interval that corresponds to their completed age. Here, we used the term delay if a child did not attain one or more of the milestones on or before the interval that corresponds to his or her completed age.

The patients whose development levels are between 0 and +2 SD and >+2 SD are classified as having "age-appropriate development," and the cases with developmental levels between −2 SD and −1 SD are grouped as having "developmental delay." Finally, the patients whose development levels are below −2 SD are grouped as having "significant developmental delay" [14]. Author permission was obtained to use the questionnaire.

Laboratory Findings and Skin Prick Test

Laboratory data that were obtained during patient follow-up for AD in the paediatric allergy clinic were retrospectively screened from the electronic medical reports. The primary outcome of the study was defining sleep patterns and the development of children with AD, and the secondary outcome of the study was to evaluate the effect of laboratory findings on sleep patterns and development. Complete blood counts, serum total IgE and specific IgE (sIgE) values of the patients were evaluated. An absolute eosinophil count (AEC) >500/μL was accepted as eosinophilia. Serum total IgE (U/L) levels were analysed by the nephelometric system (Siemens Healthcare Diagnostics, Deerfield, Germany). Serum total IgE values of the

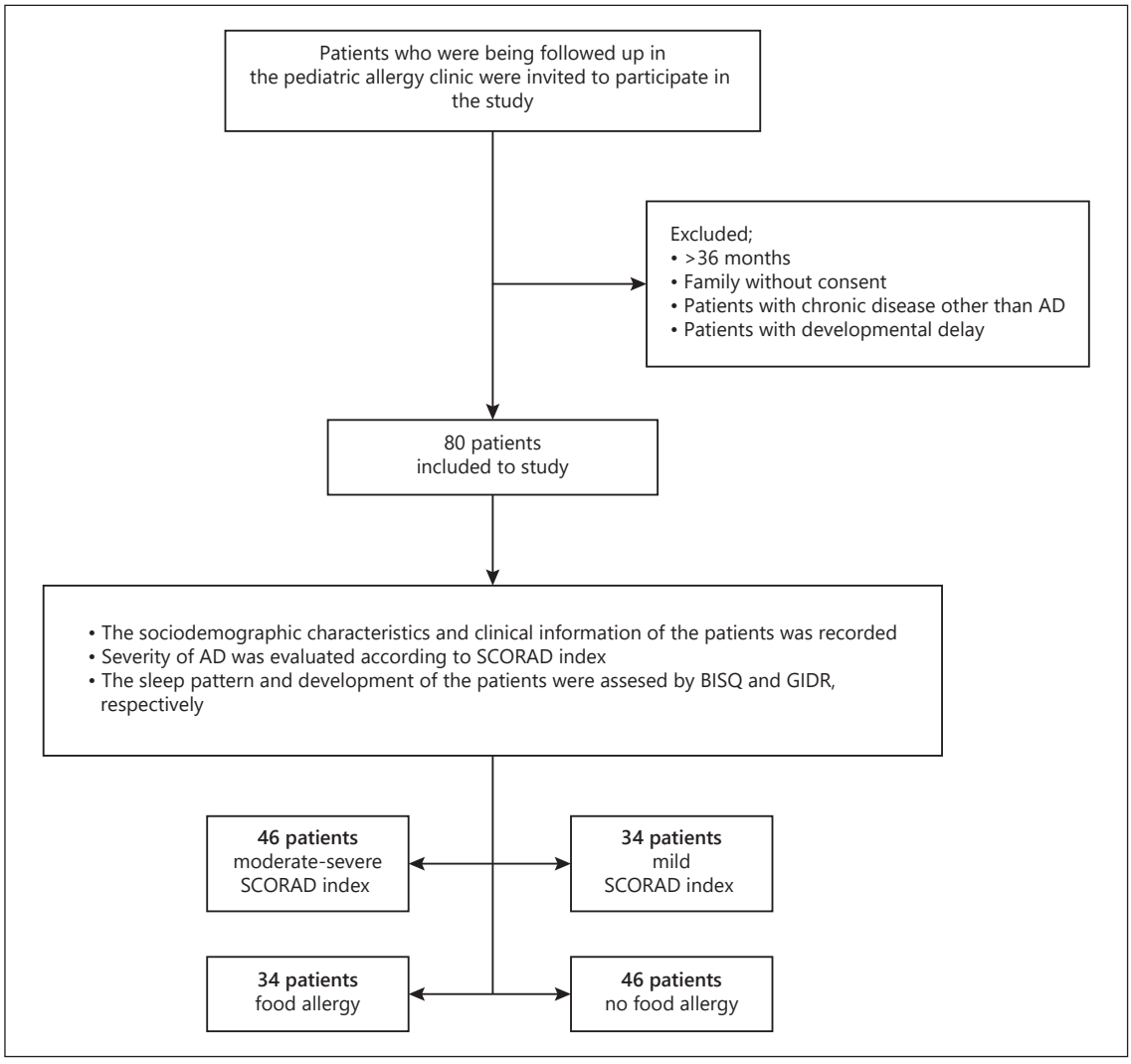

Fig. 1. Flow chart of the patients. AD, atopic dermatitis; BISQ, Brief Infant Sleep Questionnaire; GMCD, Guide for Monitoring Child Development; SCORAD, SCORing Atopic Dermatitis.

patients were evaluated according to age-specific reference intervals [15]. The determination of sIgE was measured with an enzyme immunoassay system (IMMULITE Siemens, Germany). sIgE levels (kU/L) >0.35 kU/L were considered positive. The skin prick test was performed on the back of the patients using a panel of eight major food standardized allergens (ALK-Abello, Madrid, Spain). Food allergy diagnosis was based on a positive oral food challenge test.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the research data. The χ^2 and Mann-Whitney U tests were used for non-normally distributed variables. Student's *t* test was used to compare normally distributed parametric data. Correlations were analysed using Spearman's test. Univariate and multivariate logistic regression analyses were used to evaluate risk factors. All variables obtained from the study that may be effective modifiers were used for the selection of variables when constructing the univariate logistic regression model. In univariate analysis, variables with $p < 0.20$ were determined as candidate variables. The multivariate model was constructed by performing backward stepwise regression, eliminating non-significant variables. The multivariate model for the risk factors associated with sleep problems in patients with AD was constructed, including sex (male/female), eosinophilia, SCORAD index, total IgE, breastfeeding, duration of disease (<3 months), developmental delay, and delay in gross motor skills. The multivariate model for the risk factors associated with developmental delay in patients with AD was constructed, including sex (male/female), number of siblings (>1), family history of atopy, patient receiving treatment, food allergy, eosinophilia, SCORAD index, total IgE, breastfeeding, duration of disease (<3 months), sleep problems, night waking (>3 times), staying awake at night (>1 h), and total duration of sleep (<9 h). A value of $p < 0.05$ was considered significant.

Table 1. Demographic characteristics of the children with atopic dermatitis

Demographic characteristics	*N* (%)
Sex	
Male	51 (63.7)
Median age, months	6 (4.25–9)[b]
Gestation age	
Term	70 (87.5)
Late preterm	10 (22.5)
Number of siblings	
≥1 sibling	44 (55)
Single child	36 (45)
Feeding (first 6 months)	
Breastfeeding	61 (76.3)
Formula±breastfeeding	19 (238)
Family history of atopy	24 (30)
Maternal age, year	28.04±4.9[a]
Paternal age, year	31.60±5.4[a]
Maternal educational status	
Primary school	20 (25)
High school	30 (37.5)
University	30 (37.5)

[a] Mean±standard deviation. [b] Median (IQR).

Table 2. Sleep periods of patients with atopic dermatitis

	All patients (n = 80)	Patients with sleep problems (n = 40)
Number of night wakings[a]	3.08±1.58	4.33±1.16
Nocturnal wakefulness time[b]	30 (20–65)	60 (30–90)
Daytime sleep time[b]	120 (60–240)	90 (60–180)
Nocturnal sleep time[a]	504.38±93.11	464.25±91.5
Total sleep duration[a]	646±133.31	578±121.83

[a] Mean±standard deviation. [b] Median (IQR).

Results

Patient Characteristics

The demographic characteristics of the 80 patients included in the study are shown in Table 1. Atopy (skin prick test and/or sIgE positivity) was found in 50% of the patients. Food allergy was detected in 42.5% of all patients. The presence of food allergy was positively correlated with AEC and total IgE (p = 0.001, r = 0.361 and p = 0.037, r = 0.233, respectively). AEC was significantly higher in patients with moderate-severe AD (p = 0.007). Sleep problems were more frequent in patients with moderate-severe AD (OR, 2.85; 95% CI, 1.13–7.15, p = 0.024). There was a positive correlation both between the SCORAD index and number of night wakings (p = 0.009, r = 0.289) and between the SCORAD index and nocturnal wakefulness time (p = 0.002, r = 0.347). There was a negative correlation between the SCORAD index and continuous nocturnal sleep time (p = 0.022, r = −0.255). There was no correlation between the SCORAD index and developmental delay (p = 0.864).

Sleep Patterns of the Patients

Participants frequently fell asleep by rocking (60%) and breastfeeding (56%). In all, 83.8% of the patients were sleeping in their parents' rooms, and 53.8% of the patients were sleeping in the supine position. The sleep periods of patients with AD are shown in Table 2. According to the BISQ, 50% of the patients with AD had sleep problems. The sleep problems of patients with AD are shown in Figure 2.

In our study group, 45% of the mothers thought that their children had sleep problems. In 40 patients with sleep problems, only 65% of them were described to have sleep problems according to their mothers' statements. It was found that 72.5% of the patients with sleep problems were male, 87.5% were term, and 50% had multiple siblings. It was found that boys woke up more than girls at night (p = 0.024). Sleep problems were significantly higher in patients with AD who were in the first 3 months of diagnosis, in patients with moderate-severe AD, and in patients with eosinophilia (OR, 2.51; 95% CI, 1.01–6.19, p = 0.044; OR, 2.85; 95% CI, 1.13–7.15, p = 0.024; and OR, 3.56; 95% CI, 1.40–9.08, p = 0.013, respectively). Univariate and multivariate logistic regression analyses were performed to determine the risk factors associated with sleep problems (Table 3). As a result of multivariate logistic regression analysis of factors associated with sleep problems, male sex (OR: 3.78; 95% CI, 0.083–0.837, p = 0.024), patients with AD who were in the first 3 months of diagnosis (OR: 3.56; 95% CI, 1.220–10.43, p = 0.020), and moderate-severe AD (OR: 5.09, p = 0.005, 95% CI, 1.649–15.748) were determined as risk factors for sleep problems.

Development of the Patients

In all, 12.5% of the patients had developmental delay, with 30% of these patients having significant developmental delay. In patients with developmental delay, 70, 30, 20, 10, 10, and 10% of them had developmental delay in gross motor skills, in expressive language and communication, in receptive language, in fine motor skills, in a relationship, and in play, respectively. Developmen-

Table 3. Determination of risk factors associated with sleep problems in children with atopic dermatitis by logistic regression analysis

	Univariate	Multivariate		
	OR (95% GA)	*p*	OR (95% GA) (*N*: 78)	*p* value
Sex (male)	2.155 (0.849–5.481)	0.106	3.787 (0.083–0.837)	**0.024**
Breastfeeding	0.495 (0.172–1.428)	0.193	–	
Duration of disease (<3 months)	2.513 (1.019–6.198)	**0.045**	3.567 (1.220–10.431)	**0.020**
Eosinophilia	3.157 (1.255–7.938)	**0.015**	–	
Total IgE	0.495 (0.172–1.428)	0.193	–	
SCORAD index	2.852 (1.137–7.152)	**0.025**	5.096 (1.649–15.748)	**0.005**
Developmental delay	4.750 (0.941–23.985)	**0.059**	5.533 (1.031–29.705)[a]	**0.094**[a]
Delay in gross motor skills	6.882 (0.789–60.060)	0.081	–	

SCORAD, SCORing Atopic Dermatitis. [a] Given within 90% confidence interval. *p* values less than 0.05 are shown in bold.

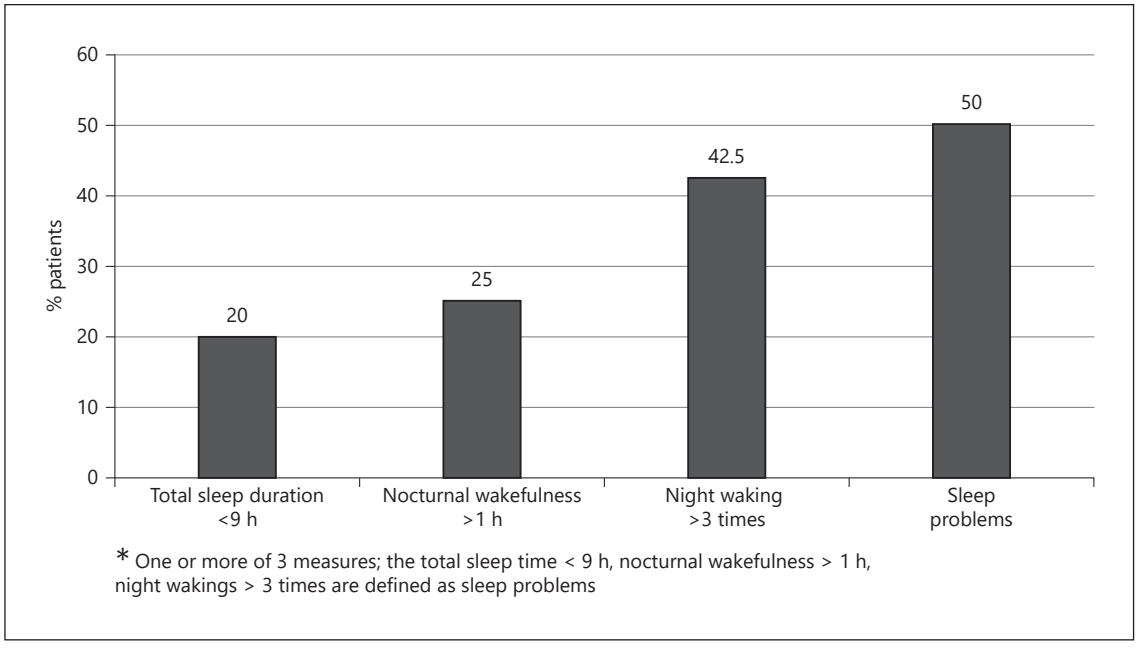

Fig. 2. Sleep problems of patients with atopic dermatitis.

tal delay was more frequent in patients with multiple siblings and in patients with sleep problems (OR, 14.3; 95% CI, 1.71–119.5, $p = 0.004$; OR, 4.75; 95% CI, 0.94–23.9, $p = 0.037$, respectively). The presence of food allergy, eosinophilia, night wakings >3 times, and the children of mothers with primary/secondary school graduates had a more significant delay in gross motor skills (OR, 9.64; 95% CI, 1.10–84.3, $p = 0.038$; OR, 9.10; 95% CI, 104–79.5, $p = 0.039$; OR, 9,64; 95% CI, 1.10–84.3, $p = 0.037$; and OR, 9.66; 95% CI, 1.70–54.81, $p = 0.009$, respectively). Univariate and multivariate logistic regression analyses were performed to determine the risk factors associated with developmental delay (Table 4). As a result of multivariate logistic regression analysis of factors associated with developmental delay, multiple siblings (OR: 14.381; 95% CI, 1.557–132.87, $p = 0.019$) and the presence of sleep problems (OR: 8.011; 95% CI, 1.764–36.387, $p = 0.024$) were found to be risk factors for developmental delay.

Table 4. Determination of the risk factors associated with developmental delay in children with AD by logistic regression analysis

	Univariate		Multivariate	
	OR (95% GA)	*p*	OR (95% GA)	*p* value
Sex (male)	0.286 (0.031–2.343)	0.234	–	–
Number of siblings (>1)	8.600 (0.984–75.151)	**0.019**	14.381 (1.557–132.871)	**0.019**
Family history of atopy	1.857 (0.382–9.020)	0.443	–	–
Breastfeeding	1.318 (0.234–7.412)	0.754	–	
Duration of disease (<3 months)	3.203 (0.583–17.600)	0.181	–	–
Patients receiving treatment	0.654 (0.137–3.130)	0.595	–	–
Food allergy	9.643 (1.102–84.365)	**0.041**	4.470 (1.104–18.096)	**0.078**[a]
Eosinophilia	9.103 (1.041–79.594)	**0.046**	–	–
Total IgE	1.318 (0.234–7.412)	0.754	–	–
SCORAD index	0.984 (0.205–4.717)	0.984	–	–
Sleep problems	6.882 (0.789–60.060)	**0.081**	–	–
Night-time waking >3 times	9.643 (1.102–84.365)	**0.041**	8.011 (1.764–36.387)	**0.024**
Staying awake at night >1 h	0.474 (0.054–4.193)	0.502	–	–
Total duration of sleep ≤9 h	1.686 (0.296–9.607)	0.556	–	–

AD, atopic dermatitis; SCORAD, SCORing Atopic Dermatitis. [a] Given within 90% confidence interval. *p* values less than 0.05 are shown in bold.

Discussion/Conclusion

To our knowledge, this is the first study evaluating both sleep patterns and the development of children aged 0–36 months with AD. Although there have been studies in the literature investigating the effects of AD on sleep [6, 16], there is no study about the sleep and development of children with AD together at an early age. The key findings of our study indicate that sleep patterns and the development of children with AD may be affected at an early age.

Children with AD have increased sleep problems [6, 17]. In 2 different studies evaluating sleep problems in healthy children aged 0–3 years, the presence of sleep problems was found to be 10 and 28.5%, respectively [18, 19]. Hon et al. [20] reported that 47% of children with AD had sleep problems. Sleep problems were higher in our patients compared to the studies that researched sleep problems in healthy children of similar age.

In 17.5% of our patients, sleep latency was longer than 1 h. Başkale and Turan [21] found that 9.2% of healthy children aged 0–3 years fell asleep for >1 h. Chang et al. [6] found that the sleep latency of patients with AD was longer (45 ± 29.3 min) than those in the healthy group, and they had more night wakings. We compared the sleep patterns of our study group and healthy children of similar age reported from the study of Taşdemir and Bayık Temel [18]. The total sleep time in children with AD decreased by 1.5 h, the frequency of night waking was 2 times higher, and the mean nocturnal wakefulness time was 40 min longer in our patients compared to the healthy group. Our study supports reports showing that the frequency of night waking and nocturnal wakefulness time are increased in patients with AD [6, 17]. Similar to previous studies, our study has shown that as the severity of the disease increases (moderate-severe AD), the total sleep time decreases and both the frequency of night waking and nocturnal wakefulness time increases [6, 16].

Maternal perception of sleep problems in children varies across cultures [22, 23]. Sleep problems that were confirmed by the BISQ were significantly higher in children who were thought to have sleep problems according to their mothers. Mothers' perception was good in detecting sleep problems, but by using the BISQ, sleep problems were found in 31% of the patients whose mothers were thought to have no sleep problems. We suggest that since sleep problems in early childhood may have an impact on development and neurocognitive functions [7], objective tools are needed to evaluate the sleep of children.

The effect of sex on sleep problems in children varies in the literature. Some studies reported no difference in the frequency of sleep problems according to sex [7, 18], but there are also studies supporting that sleep problems are more common in boys, which is similar to our study [24].

We found that our patients within the first 3 months after diagnosis had more sleep problems. The decrease in sleep problems 3 months after diagnosis may be a result of the regulation of environmental factors, avoidance of triggers, medical treatment, and family adaption. Three months after diagnosis, 39.5% of our patients still had sleep problems. This rate was higher than the frequency of sleep problems in healthy children [18, 19]. As a result, it was revealed that although the sleep problems of the patients decreased during the follow-up, these problems persisted due to the learnt abnormal sleep patterns. In addition, Reuveni et al. [17] observed sleep fragmentation in children with AD in clinical remission. It has been reported that pruritus, in the active phase of the disease, may cause sleep disruption, and the itching sensation during clinical remission may induce arousals and awakenings without active scratching. Additionally, learnt sleep behaviours as a result of AD may cause sleep disruptions in the future [17].

Sleep deprivation during early childhood is known to have negative effects on cognitive and behavioural development [7, 8, 25]. It has been shown that infant eczema with concurrent sleeping problems appears to be a risk factor for the development of mental health problems by the age of 10 [26]. Camfferman et al. [27] reported worse sleep quality and significant neurocognitive deficits in children with eczema. In our patients, the developmental delay was significantly increased in the group with sleep problems.

A relationship between sleep efficiency and cognitive gains has been established in a study evaluating the effect of sleep on cognitive development in infants [7]. In the study, it was observed that the infants who had more motor activity in sleep and a more fragmented sleep pattern were moderately associated with a lower mental developmental index. In addition, similar to our study, cognitive gains were found to correlate with sleep regulation (e.g., sleep fragmentation) rather than circadian sleep measurements (e.g., sleep onset time and duration).

In our patients, the frequency of waking up at night affected the development in the area of gross motor skills, but there was no significant relationship between total sleep time, difficulty in falling asleep and night waking time and developmental delay. In the study by Meldrum et al. [28], it was shown that composite motor skills at 18 months (a combined score based on fine and gross motor skills) were significantly lower in the children with allergic diseases and/or a diagnosis of eczema at 12 months of age. Furthermore, children with eczema appear to have relatively poorer gross motor skills in particular, as the major contributor to the composite motor score findings. Meldrum et al. [28] reported that a food allergy affects behaviour scores. In our study, the delay in gross motor skills was higher in patients with a food allergy.

In our study group, we found that those with multiple siblings had more developmental delay. Similarly, there are studies supporting the negative effects of crowded families on cognitive development [29, 30]. The delay in gross motor skills was higher in children with low maternal education levels. Ramazan and Demir [31] found that as the education level of mothers increases, the cognitive development level of the children increases. We think that multiple siblings and the low level of maternal education may adversely affect the development due to stimulus deprivation. However, as a result of multivariate regression analysis, low mother education was not found to be a risk factor for developmental delay [15].

The main limitation of our study is that the healthy control group was not included in the study. Since the sleep questionnaire has validity in the age group 0–36 months, our sample size was limited to this age group. Another limitation is that the results are based on subjective parental reports. Parents' reports may cause potential bias because parents may be affected by anxiety/stress caused by chronic health conditions, such as AD.

The strengths of our study were that the number of targets at the power analysis has been reached. The BISQ and GMCD have validity in Turkey and are made by the same observer. Our study is the first study in the literature that evaluates the sleep patterns and development of patients aged 0–36 months who have AD.

Boys with moderate-severe AD within the first 3 months after diagnosis were at increased risk for sleep problems. Mothers' perception was good but insufficient in detecting sleep problems. Because sleep problems in early childhood may have an impact on development and neurocognitive functions [7], objective tools are needed to evaluate the sleep of children. Children with AD who have sleep problems and multiple siblings should be closely monitored in terms of developmental delay, particularly in the area of gross motor skills. When sleep problems and developmental delay are detected in the early period, behavioural and cognitive disorders that may develop in the following years can be prevented with appropriate recommendations and interventions.

In conclusion, this study provides further evidence between sleep patterns and the development of children with AD. While our data support the notion that sleep

patterns and development of children with AD may be affected at an early age, other more complex interactions cannot be excluded. Our findings emphasize that more research is needed on the development of children with AD, especially in children with sleep problems.

Statement of Ethics

Ethics committee for clinical research of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, University of Health Sciences, Date; February 25, 2018 protocol code; 2019-015.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shared authorship contributed equally.

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