Prevalence and Related Factors of Attention Deficit Hyperactivity Disorder in School-age Children With Atopic Dermatitis

Haomiao Yu, BMed; Weicong Zhang, BMed

ABSTRACT

Context • Atopic dermatitis (AD) is a chronic inflammatory skin disease and commonly affects children. AD is associated with a high incidence of ADHD, the most common psychological and neurobehavioral disorder in children and adolescents. If clinicians don’t identify ADHD and intervene early, preschool children can experience adverse effects.

Objective • The study intended to investigate the prevalence of attention deficit hyperactivity disorder (ADHD) in preschool children with AD, analyze the associated factors, and provide insights for early identification of risk factors and the development of interventions to reduce the likelihood of ADHD occurrence.

Design • The research team performed a prospective, observational, case-control study.

Setting • The study took place at the Zhoushan branch of Ruijin Hospital at the Shanghai Jiaotong University School of Medicine in Zhoushan, Zhejiang, China.

Participants • Participants were 80 school-aged children diagnosed with AD and admitted to the hospital between May 2019 and May 2023.

Groups • Based on the presence or absence of ADHD, the research team divided the children into two groups: (1) the Simple AD group with 71 participants with AD only, and the AD + ADHD group, with 9 participants with AD and ADHD.

Outcome Measures • The research team: (1) collected and analyzed participants’ demographic and clinical data, including an assessment of the AD severity using the SCORing Atopic Dermatitis (SCORAD) scale and the presence of sleep disorders using the Children’s Sleep Habits Questionnaire (CSHQ); (2) assessed the presence of ADHD using the Swanson, Nolan, and Pelham-IV rating scales (SNAP-IV); (3) analyzed the factors influencing the occurrence of ADHD in AD children, using univariate and multivariate logistic regression analysis.

Results • Among the 80 school-age children with AD, 9 participants (11.25%) had received a diagnosis of ADHD. The AD + ADHD group's age (P < .001); body mass index (BMI), with P < .001; AD severity (P = .013); rate of sleep disorders (P = .001); and levels of serum interleukin 6 (IL-6), with (P < .001), interleukin 4 (IL-4), with (P < .001), and nerve growth factor (NGF), with (P < .001) were all significantly greater than those of the Simple AD group. The univariate logistic regression analysis indicated that age (P = .014), BMI (P = .024), AD severity (P = .022), sleep disorders (P = .042), and levels of IL-6 (P = .044), IL-4 (P = .045), and NGF (P = .046) were all significantly related to the development of ADHD in school-age children with AD. The multivariate logistic regression analysis revealed that sleep disorders (P = .018) and elevated levels of serum IL-6 (P = .032), IL-4 (P = .021), and NGF (P = .016) were independent risk factors for ADHD (OR = 2.651, 3.074, 2.686, 3.340).

Conclusions • School-aged children with AD are more likely to develop ADHD, which is mainly associated with sleep disorders and elevated levels of serum IL-6, IL-4, and NGF. Clinicians should give attention to these risk factors and implement early interventions to reduce the risk of children with AD developing ADHD. (Altern Ther Health Med. [E-pub ahead of print.])

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Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease associated with a genetic predisposition to allergies. In recent years, with the rapid urbanization and lifestyle changes in China, the incidence of AD in children aged 1-7 years was 12.94%, and the incidence of children under 1 year old was up to 30.48%.

AD commonly affects children, and itching, polymorphic skin lesions and a tendency to exude characterize it. The intense itching and discomfort from skin lesions can lead to stress, lowered self-esteem, and potentially, anxiety or...
depressive symptoms.2 Visible skin symptoms can lead to stigmatization, reducing opportunities for social interactions and affecting interpersonal skill development.3 Also, asthma and allergic rhinitis often accompany AD.4 AD significantly impacts the growth, development, and overall well-being of affected children1,2,5; it affects their psychological well-being, daily functioning, academic performance, and social interactions.6

AD and ADHD

Minamoto and Patsatsi found that children with AD are closely associated with psychological and behavioral problems, with a higher incidence of comorbidities, such as attention deficit hyperactivity disorder (ADHD), anxiety, and depression.6,7 Among those comorbidities, ADHD is the most common psychological and neurobehavioral disorder in children and adolescents, characterized by age-inappropriate levels of inattention, hyperactivity, impulsivity, and learning difficulties, with a prevalence rate of up to 5%.3,4,8

Considering that school-aged children with AD often have symptoms of inattention, frequent temper outbursts, and conflicts with teachers and peers, their emotional instability and increased psychological stress may affect the hypothalamic-pituitary-adrenal axis, leading to increased secretion of norepinephrine and resulting in cognitive dysfunction and ultimately triggering ADHD.9 If clinicians don’t identify ADHD and intervene early, it can have serious adverse effects on preschool children’s psychological, daily functioning, academic performance, and social interactions.

Possible Predictive Indicators

Clinicians and researchers have extensively explored the association between AD and ADHD. Complex interrelationships exist between them, such as genetic factors, inflammatory responses, and lifestyles. Tong found that patients with AD are more likely to develop ADHD, which imposes a burden on both the individual and society.10 Some research has indicate possible predictive indicators: (1) sleep disorders, (2) the inflammatory cytokines interleukin 6 (IL-6) and IL-4 and (3) nerve growth factor (NGF).

Sleep disorders. Children with AD often experience worse skin itching and frequent scratching during the night, leading to sleep disorders, such as difficulty falling asleep and insufficient sleep. These sleep disturbances can result in a range of behavioral changes, including inattention, memory decline, and daytime emotional disturbances, which are consistent with ADHD’s symptoms.11

Reguiai and Becherel found that sleep disorders could interact with inflammatory factors, affecting brain development in children with ADHD, particularly in the prefrontal cortex and neural systems related to arousal regulation, which can contribute to ADHD.12 Tang et al also indicated that sleep disorders can be the main triggers for the coexistence of ADHD in children with AD.9

IL-6 and IL-4. As a multifunctional cytokine, IL-6 plays a role in immunity and neurotransmitters and may affect the pathological mechanisms of ADHD. As an anti-inflammatory cytokine, IL-4 may regulate the balance of immunity and neurotransmitters and affect the association between AD and ADHD.

Lin et al demonstrated a potential relationship between inflammatory cytokines and ADHD in children with AD, with IL-6 and IL-4 being commonly observed.13 During the course of AD, the secretion of inflammatory cytokines such as IL-6 and IL-4 increases.14 These cytokines can cross the blood-brain barrier and activate neuroimmune mechanisms associated with behavioral and emotional circuits related to ADHD as well as affect the development of cognitive and attention-related prefrontal cortex areas.15 Therefore, the elevation of inflammatory cytokine levels can directly or indirectly affect ADHD-related brain regions, leading to the occurrence of ADHD.16

NGF. NGF is a nerve growth factor that affects neural survival and growth and may be associated with neurological abnormalities in AD and ADHD. Ertus have found that the immune system plays a role in allergic inflammation, and allergic diseases are one of the factors contributing to the development of ADHD.17 Serum NGF acts as a carrier for the interaction between the immune and nervous systems and plays a critical role in controlling allergic inflammatory responses.15

An increased level of NGF enhances inflammatory responses, thereby increasing the risk of ADHD.18 Komaki et al also found that serum NGF levels were abnormally elevated in children with ADHD, further suggesting the involvement of NGF in the progression of ADHD.18

Current Studies

The current study aimed to investigate the prevalence of ADHD in preschool children with AD, analyze the associated factors, and provide insights for early identification of risk factors and the development of interventions to reduce the likelihood of ADHD occurrence.

METHODS

Participants

The research team performed a prospective, observational, case-control study, which took place at the Zhoushan branch of Ruijin Hospital at the Shanghai Jiaotong University School of Medicine in Zhoushan, Zhejiang, China. Potential participants were school-aged children admitted to the hospital between May 2019 and May 2023. The participants for this study were recruited by the research team at the Zhoushan branch of Ruijin Hospital, affiliated with the Shanghai Jiaotong University School of Medicine in Zhoushan, Zhejiang, China. The team collaborated with the hospital staff, including doctors and nurses, to identify school-aged children who met the criteria for enrollment. Potential participants were identified, the research team contacted them or their parents/guardians to explain the study and obtain informed consent. The initial contact may have been made through face-to-face meetings, telephone conversations, or written communication. During these interactions, the research team provided detailed
information about the study's purpose, design, procedures, and potential risks and benefits. Emphasizing that participation was voluntary, participants or their parents/guardians were informed of their right to decline or withdraw from the study any time.

The study included participants if they: (1) were between 6 and 12 years of age, and (2) had received a diagnosis of AD according to the diagnostic criteria. The diagnostic criteria: 1) Symmetrical atopic dermatitis lasting for more than 6 months. 2) Personal history of atopy and/or family history, including eczema, allergic rhinitis, asthma, allergic conjunctivitis, and chronic urticaria. 3) Elevated serum total IgE levels and/or increased peripheral blood eosinophils, and/or positive allergen-specific IgE.

The study excluded participants if they had: (1) other nonallergic, chronic diseases; (2) significant organ dysfunction, or (3) immune dysfunction.

The research team selected the above criteria based on current clinical practice and relevant research. Using the diagnostic criteria helps to ensure that the included patients all truly have AD, thereby improving the study's reliability. Past studies have established diagnostic criteria for AD, which helps to clarify the selection of cases.

The children's guardians signed informed consent forms. The hospital's Ethics Committee approved the study's protocols. This study is consistent with the Declaration of Helsinki.

Procedures

Data collection. The research team used a self-designed questionnaire to collect demographic and clinical information based on the research objectives. The questionnaire included age, gender, body mass index (BMI), mode of birth, severity of AD, duration of mother's breastfeeding, gestational age at birth, and sleep disorders.

Quality control. All investigators received standardized training and informed the children and their guardians about the purpose of the study and the instructions for completing the questionnaire. After completing the questionnaires, the investigators collected them immediately. Two professionals from the hospital cross-checked the collected data to ensure accuracy before using the research team used the data for the statistical analysis.

Groups. Based on the presence or absence of ADHD, the research team divided the participants into two groups: (1) the simple AD group, who had AD only, and the AD + ADHD group, who had AD and ADHD.

Serum markers. The research team: (1) collected 3 mL of fasting venous blood from all patients upon admission; (2) after centrifugation, separated the upper serum layer and stored it for further analysis; and (3) used enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Minneapolis, Minnesota, USA) to measure the levels of IL-6, IL-4, and NGF in the serum.

The research team: (1) allowed the collected blood sample to stand at room temperature for 30 min and then centrifuged it to separate the serum; (2) performed the assays using the ELISA kits, according to the manufacturer's instructions; (3) added standard curve samples and control groups; (4) for IL-6, IL-4, and NGF, used double-antibody sandwich assays from R&D Systems (Minneapolis, Minnesota, USA); (5) after the assays, applied the HRP-conjugated secondary antibodies (HRP-conjugated secondary antibodies) to TMB to produce a color reaction, and (6) determined the concentrations of IL-6, IL-4, and NGF in the samples based on the color's optical density.

Data analysis. This analysis involved several key processes in ELISA. Firstly, standard curves were constructed by preparing a series of known concentrations of the target analyte. These standards were incubated and processed alongside the samples, and their optical density values were measured using a spectrophotometer. A standard curve was then generated by plotting the optical density values against the known concentrations. Secondly, optical density was determined by measuring the absorbance of light passing through the samples using a spectrophotometer. Lastly, measurements obtained from the control group were compared with those from other groups to assess differences or similarities in analyte levels. These processes collectively enabled quantification and comparison of the target analyte in this study.

Outcome Measures. The research team: (1) collected and analyzed participants' demographic and clinical data, including an assessment of AD severity using the SCORing Atopic Dermatitis (SCORAD) scale and the presence of sleep disorders using the Children's Sleep Habits Questionnaire (CSHQ); (2) assessed the presence of ADHD using the Swanson, Nolan, and Pelham-IV rating scales (SNAP-IV); (3) analyzed the factors influencing the occurrence of ADHD in AD children, using univariate and multivariate logistic regression analysis.

Outcome Measures

AD severity. The SCORAD scale includes three dimensions: extent of skin lesions, intensity of skin lesions, and subjective symptoms.

Total score = extent of skin lesions/5 + intensity of skin lesions/2 + subjective symptoms (0-103 points). Scores of 0-24 = mild, 25-50 = moderate, and > 50 = severe AD.

Sleep disorders. The CSHQ evaluates sleep patterns. The questionnaire consists of 33 items across eight dimensions, scored on a scale of 1-3, with 1 = 0-1 times per week, 2 = 2-4 times per week, and 3 = 5-7 times per week. Higher scores indicate more pronounced sleep disorders. A total score above 41 indicates the presence of sleep disorders.

ADHD. The SNAP-IV consists of 26 items rated on a scale from 0 to 3, with scores ranging from 0 = not at all to 3 = very much. The total score ranges from 0 to 76, and dividing the total score by the number of items obtains the average score. Average scores of 0-1 = normal, 1.1-1.5 = borderline, 1.6-2 = moderate, and > 2 = severe ADHD. A score between 1.1 and 1.5 with at least 5 items scored as 2, or moderate, and/or 3, severe, confirms a diagnosis of ADHD.
Univariate logistic regression analysis. The research team conducted the univariate logistic regression analysis using the factors that showed statistically significant differences in the analysis of the collected demographic and clinical data.

Multivariate logistic regression analysis. The research team used the presence of ADHD as the dependent variable—ADHD = 1 and no ADHD = 0 and included the factors that showed significant differences in the univariate analysis as the independent variables. The team treated age, BMI, serum IL-6, IL-4, and NGF as continuous variables, and coded AD severity as severe = 1 and mild/moderate = 0 and the presence of sleep disorders as yes = 1 and no = 0.

Statistical Analysis
The research team analyzed the data using the Statistical Package for Social Science (SPSS) 22.0 software (IBM, Armonk, NY, USA). The team: (1) expressed the categorical data as numbers (N) and percentages (%) and compared the groups using the Chi-square ($\chi^2$) test, (2) expressed the normally distributed continuous data as means ± standard deviations (SDs) and compared the groups using Two independent sample t test, (3) performed univariate and multivariate logistic regression analyses to identify factors associated with ADHD in school-aged children with AD. $P < .05$ indicated a statistically significant difference.

RESULTS
Participants
The study included and analyzed the data of 80 participants (Table 1 and Figure 1), with 71 in the Simple AD group and 9 in the AD + ADHD group. The AD + ADHD group included five males (55.56%) and 4 females (44.44%), and the Simple AD group included 34 males (47.89%) and 37 females (52.11%). The AD + ADHD group’s mean age was 9.29 ± 1.07 years, with a range of 6 to 12 years, and was significantly older than that of the Simple AD group, at 8.12 ± 0.82 years, with a range of 6 to 12 years ($P < .001$).

The AD + ADHD group’s BMI was 21.73 ± 2.05 kg/m$^2$, which was significantly higher than that of the Simple AD group, at 19.88 ± 1.24 kg/m$^2$ ($P < .001$). The AD + ADHD group’s rate of participants meeting the AD severity level of severe, with 6 participants (66.67%), was significantly higher than that of the Simple AD group, with 15 participants (21.13%), with $P = .013$.

The AD + ADHD group’s rate of sleep disorders, with eight children having them (88.89%), was significantly higher than that of the Simple AD group, with 24 children having them (33.80%), with $P = .001$.

The AD + ADHD group’s levels of IL-6, IL-4, and NGF, at 47.55 ± 4.32 ng/ml, 5.72 ± 1.50 ng/ml, and 99.41 ± 6.85 pg/ml, respectively, were significantly higher than those of the Simple AD group, at 28.54 ± 3.61 ng/ml, 1.26 ± 0.21 ng/ml, and 71.23 ± 5.63 pg/ml, respectively (all $P < .001$).

No significant differences existed between the groups for gender, mode of birth, duration of breastfeeding, or gestational age.

Figure 1. Comparison of Significant Factors Between the Simple AD group and the AD + ADHD group. Figure 1A shows age in years; Figure 1B shows BMI (kg/m$^2$); Figure 1C shows IL-6 (ng/L); Figure 1D shows IL-4 (ng/ml); and Figure 1E shows NGF (pg/ml).

Table 1. Comparison of Relevant Data Between School-aged Children with Simple AD and Those With Combined ADHD (N = 80)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simple AD Group n = 71 Mean ± SD n (%)</th>
<th>AD and ADHD Group n = 9 Mean ± SD n (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>8 (100.00) 8.12 ± 0.82</td>
<td>8.92 ± 1.07</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Range</td>
<td>6-12</td>
<td>6-12</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>53 (74.60) 34 (47.99)</td>
<td>.018</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>18 (25.40) 27 (37.11)</td>
<td>0.665</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of Birth</td>
<td>Term birth</td>
<td>24 (33.46) 15 (21.13)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Caesarean section</td>
<td>47 (66.14) 24 (33.87)</td>
<td></td>
</tr>
<tr>
<td>Birthplace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD severity</td>
<td>Severe</td>
<td>25 (35.0) 15 (21.13)</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>46 (64.5) 26 (36.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>33 (46.5) 21 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Duration of Breastfeeding, mos</td>
<td>≤6</td>
<td>33 (46.5) 21 (29.6)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>38 (53.5) 29 (40.4)</td>
<td></td>
</tr>
<tr>
<td>Gestational Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature birth</td>
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<td>.001</td>
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<tr>
<td>Term birth</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td></td>
<td></td>
<td>.010</td>
</tr>
</tbody>
</table>

The univariate analysis found that an older age ($P = .014$), a high BMI ($P = .024$), a rating of severe for AD severity ($P = .022$), the presence of sleep disorders ($P = .042$), and elevated levels of IL-6 ($P = .044$), IL-4 ($P = .045$), and

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Abbreviations: AD, atopic dermatitis; ADHD, attention deficit hyperactivity disorder; BMI, body mass index; IL-4, interleukin 4; IL-6, interleukin 6; NGF, nerve growth factor.

Univariate Analysis
The univariate analysis found that an older age ($P = .014$), a high BMI ($P = .024$), a rating of severe for AD severity ($P = .022$), the presence of sleep disorders ($P = .042$), and elevated levels of IL-6 ($P = .044$), IL-4 ($P = .045$), and
**Table 2. Univariate Logistic Regression Analysis of Factors Influencing ADHD in School-aged Children with AD**

<table>
<thead>
<tr>
<th>Factors</th>
<th>β</th>
<th>SE</th>
<th>Wald χ²</th>
<th>OR</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>0.786</td>
<td>0.427</td>
<td>3.586</td>
<td>1.295</td>
<td>0.950-1.744</td>
<td>.096</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>0.841</td>
<td>0.469</td>
<td>2.319</td>
<td>1.923</td>
<td>0.976-3.782</td>
<td>.074</td>
</tr>
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<td>Sleep disorders</td>
<td>0.919</td>
<td>0.491</td>
<td>4.040</td>
<td>2.588</td>
<td>1.206-5.493</td>
<td>.047</td>
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<td>Serum IL-6 (ng/mL)</td>
<td>1.123</td>
<td>0.522</td>
<td>3.665</td>
<td>2.686</td>
<td>1.509-4.851</td>
<td>.021</td>
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<td>0.500</td>
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<td>1.509-4.851</td>
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**Table 3. Multivariate Logistic Regression Analysis of Risk Factors Influencing ADHD in School-aged Children with AD**

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