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Correlation Analysis Between Children with Atopic Dermatitis and Asthma and Factors Affecting Intestinal Flora

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Abstract: *Objective:* In order to reveal the potential association between intestinal flora and atopic dermatitis with asthma, the study compares the changes in intestinal flora before and after treatment with antibiotics in children and explores the risk factors for the disease development in children. The differences between asthma-controlled children and healthy children were also analyzed to investigate whether there was a correlation between the level of control and intestinal flora in asthmatic children. *Methods:* 367 children with atopic dermatitis and asthma were selected, and the control group was healthy children who did not have other skin diseases. Fecal samples were collected from healthy children and children with asthma, and the intestinal flora was tested at Beijing Nebula Medical Testing Laboratory Co. At the same time, 50 children were selected according to the inclusion and exclusion criteria to take amide antibiotics during hospitalization, and stool samples were collected before and after taking antibiotics. *Results:* The proportion of Gram-positive cocci increased and the proportion of Gram-positive bacilli decreased after the administration of antibiotics in children with atopic dermatitis and asthma ($P < 0.05$), and no significant difference was shown in the gender and age of the children ($P > 0.05$). The proportion of family history of atopic dermatitis with asthma was higher in the experimental group ($P < 0.05$). *Conclusion:* The use of antibiotics in children with atopic dermatitis with asthma showed a positive correlation with changes in intestinal flora. The use of antibiotics may lead to changes in intestinal flora and increase the risk of atopic dermatitis with asthma. Antibiotic use in infancy and childhood is also recognized as a risk factor for atopic dermatitis with asthma. Therefore, the use of antibiotics should be minimized in preventing and treating atopic dermatitis with asthma.

Keywords: Atopic dermatitis; Asthma; Intestinal flora; Antibiotics; Influencing factors

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1. Introduction

Atopic dermatitis (AD) and asthma are common allergic diseases in children, and their incidence is increasing year by year, which brings a significant burden to affected children and their families. In recent years, researchers have realized the important role of intestinal flora in the occurrence and development of atopic dermatitis with asthma (ADA) [1]. The correlation between children with ADA and intestinal flora is an area of research that has attracted much attention. The interactions between the intestinal flora and the host may not only affect the immune system but may also regulate the body's response to external antigens. Therefore, exploring the correlation between children with ADA and intestinal flora is important to prevent and treat these diseases. ADA is a complex disease whose pathogenesis is not fully understood. Currently, despite some progress in studies on genetics, the environment, and the immune system, many unanswered questions remain [2,3]. Therefore, the search for new disease-influencing factors and therapeutic targets is the hotspot and demand of current research. In order to explore the correlation between children with ADA and intestinal flora, 367 children with ADA were selected, and the control group was healthy children who did not have other skin diseases; fecal samples were collected from healthy children and children with ADA to test the intestinal flora, the study aimed to reveal the potential association between intestinal flora and ADA as well as the mechanism of intestinal flora in developing ADA and to improve the children's health problems by providing new therapeutic strategies. By delving into the influencing factors and regulatory mechanisms of intestinal flora, the study is expected to identify new targets for intervention and improve the symptoms and life quality of children with ADA.

2. General information and methods

2.1. General information

367 children diagnosed with ADA were selected from August 2022 to January 2023 in the dermatology department of Jiangsu Province Hospital of Chinese Medicine. Inclusion criteria: (1) Age range of 1 to 12 years old; (2) Antibiotic use less than 3 days before admission; (3) No gastrointestinal symptoms such as constipation and diarrhea; (4) Antibiotic use after admission; and (5) No other skin diseases. The children's family members or guardians signed an informed consent form. Exclusion criteria: (1) Gastrointestinal symptoms such as constipation and diarrhea; (2) Antibiotic allergy. The control group was 185 healthy children who did not have other skin diseases and gastrointestinal symptoms such as constipation and diarrhea [4].

2.2. Methods

Subjects all had approximately 1 mL of peripheral venous blood drawn during hospitalization, preserved in EDTA anticoagulation tubes, and immediately sent to the emergency laboratory for testing using an automated blood cell analyzer. During hospitalization, 2–3 mL of venous blood was collected from children with ADA and saved in serum separator tubes to be sent to the immunization room, and electrochemiluminescence was chosen to detect serum immunoglobulin E (IgE) levels. IgE level, basophil (BASO), eosinophile granulocyte (EOS) percentage, and absolute value in the blood routine were recorded during the experimental period [5]. During hospitalization, 50 children with ADA were selected to take amide antibiotics. Before and after the administration of antibiotics, 2 g of fresh fecal samples were collected from children with ADA and healthy children, with age, name, and number registered accordingly, and stored at low temperature in a refrigerator at -81°C, and then sent to Nebula Medical Laboratory in Beijing for analysis. The samples were examined by microscopic examination of Gram-stained smears of fecal flora, and the reagent was the Gram stain solution of Jinruibao Biotechnology Co. Ltd. PREVI Color Gram automated Gram stainer and Leica DM750 biomicroscope from Germany were the instruments used, and the results were issued by the laboratory professionals. Factors influencing intestinal flora in the data profile included whether the child was an only child, living environment, duration of exclusive breastfeeding, mode of delivery, time of complementary food addition, and probiotic and antibiotic use before 12 months of age. The level of asthma control was investigated and recorded separately, taking into account the child's gender, age, presence of dust mite allergy, history of rhinitis, and family history of asthma.

2.3. Outcome measures

Normally, blood levels of IgE are low, the exact normal range may vary depending on the laboratory; in general, the normal range in adults is approximately between 0 and 100 IU/mL. Normal ranges for EOS and BASO percentages in routine blood tests are typically between 0 to 3% and 0 to 5% [6]. According to the 2015 CTS/CPS Consensus on the Diagnosis and Management of Bronchial Asthma in Preschool Children, the diagnostic criteria for bronchial asthma in children younger than 6 years of age include: (1) The child presents with recurrent episodes of wheezing, coughing, and dyspnea of a prolonged duration that requires treatment for relief. (2) The child has significant expiratory wheezing during the episodes and the wheezing symptoms are relieved by bronchodilator therapy. (3) The child has a persistent cough that is especially worse at night and in the early morning. (4) Association of symptoms with bronchial triggers: the child's symptoms were associated with bronchial triggers such as climate change, infections, exercise, exposure to pets, dust mites, and other bronchial triggers. (5) The child's first-degree relatives, such as parents, siblings, etc., have associated diseases such as asthma, eczema, or allergic rhinitis. Symptom grading for asthma control in children is usually categorized into three levels: well-controlled, partially controlled, and uncontrolled. These levels help doctors and patients assess the severity of the symptoms and response to treatment. At the well-controlled level, children's asthma symptoms are well controlled, and they have few symptoms such as breathing problems and limited activity. They can participate in school and daily activities as usual and do not need emergency medication. At the partially controlled level, children's asthma symptoms sometimes occur but are not persistent. They may need to use emergency medications to relieve acute attacks, but most of the time, their asthma symptoms can be controlled. However, they may have some activity restrictions. At the uncontrolled level, children's asthma symptoms are very pronounced and they may experience frequent shortness of breath, coughing, and chest tightness. They may require frequent use of emergency medications to relieve asthma attacks, and these symptoms may significantly impact their daily activities and life quality.

2.4. Statistical methods

The study was conducted using SPSS24.0 to statistically analyze the data, which was expressed as mean ± standard deviation (SD), and the test of chi-square and K-S normality tests were performed. Descriptive statistics were performed on the basic information including age, gender, and medical history of the children to understand the characteristics of the study sample. Independent samples *t*-test compared subgroup information, and paired samples information compared intestinal flora information before and after treatment. Correlation analysis was used to assess the relationship between clinical indicators of asthma control level and intestinal flora in children with ADA. Logistic regression analysis was used for the analysis of ADA disease risk factors, and the assessment of risk factors for ADA and the level of asthma control was performed by using the odds ratio (OR) and 95% confidence interval (CI) test. OR is commonly used in case-control studies and cohort studies to assess the strength of the relationship between a factor and a particular outcome. It can help researchers determine whether a factor is associated with a particular outcome and can provide a measure of the degree of association. In essence, it can reflect differences in exposure from controls, thus establishing a link between disease and exposure factors. Biological data statistics and analysis were done by Beijing Nebula Medical Laboratory, $P < 0.05$ was considered a statistically significant difference.

3. Results

3.1. Children with ADA and healthy children

367 children with ADA and 185 healthy children were selected for the study to compare the basic conditions

such as gender and age in **Table 1**.

Table 1. Comparison of basic information between ADA children and healthy children

Group	Gender (male/female)	Family history of ADA	IgE value (IU/mL)	EOS percentage (%)	EOS absolute value (× 10^9/L)	BASO percentage (%)	BASO absolute value (× 10^9/L)
ADA	156/211	54	139.90	1.70	0.12	0.30	0.02
Healthy	93/92	9	84.10	1.40	0.11	0.30	0.02
P value	0.08	0.001	0.000	0.297	0.248	0.918	0.964

In **Table 1**, family history of ADA disease was 4.86% in healthy children and 14.71% in children with ADA, $P = 0.001$ (< 0.05). Serum IgE value was 84.10 IU/mL in healthy children and higher in ADA children with 139.90 IU/mL, $P = 0.001$ (< 0.05). The *P* value for both the percentage and absolute value of EOS and BASO was greater than 0.05. Both the percentage and absolute value of EOS were higher in ADA than in healthy children due to the fact that EOS is a type of leukocyte that is mainly involved in fighting parasitic infections and allergic reactions. The number of EOS is elevated in certain specific situations such as allergies, asthma, parasitic infections, or other inflammatory reactions.

3.2. Changes in factors influencing intestinal flora before and after antibiotic administration in children with ADA

3.2.1. Changes in intestinal flora in children with ADA before and after antibiotic administration

During the course of treatment, all 50 children with ADA were given amide antibiotics, which are primarily bactericidal against Gram-positive and some Gram-negative bacteria, and may have strong antimicrobial effects against certain bacteria in the intestinal tract. Gram-negative cocci (GNC), Gram-positive cocci (GPC), Gram-negative bacilli (GNB), and Gram-positive bacilli (GPB) were studied, as well as the mean average number of bacteria per field of view (ABV) before and after antibiotic administration as shown in **Table 2**.

Table 2. Changes in intestinal microbiota before and after taking antibiotics

Group	GNC proportion (%)	GPC proportion (%)	GNB proportion (%)	GPB proportion (%)	ABV (/field of view)
Before antibiotics	0.5	28.37 ± 15.46	33.65 ± 14.29	37.36 ± 14.07	2822.22 ± 1164.10
After antibiotics	0.5	36.24 ± 21.60	33.59 ± 15.45	29.59 ± 14.65	2481.30 ± 1343.01
P value	0.290	0.010	0.982	0.002	0.142

ABV of ADA children before treatment was 2822.22 ± 1164.10/field of view, there was a significant decrease in ABV after taking the drug, $P = 0.142$ (> 0.05). The GPC ratio increased significantly, $P = 0.010$ (< 0.05). The GPB ratio decreased significantly, and the degree of bacterial flora disruption was exacerbated by the antibiotics, $P = 0.002$ (< 0.05). There is no change in GNC proportion before and after treatment, $P = 0.290$ (> 0.05). There is no significant change in GNB proportion before and after treatment, $P = 0.982$ (> 0.05). The intestinal flora changed after taking antibiotics, and the diversity and richness of intestinal flora decreased. GPC may cause many kinds of infections, including skin and soft tissue infections, respiratory infections, blood infections, etc. GPB can regulate the balance of intestinal flora in humans to a certain extent, improve digestion and enhance immunity. Increasing the proportion of GPC and decreasing the proportion of GPB may lead to symptoms aggravation in ADA children.

3.2.2. Effect analysis of gender and age on the intestinal flora of ADA children before and after antibiotic administration

In general, the amount of GNC in the intestinal flora is relatively small, whereas GPB occupies a major component of the flora. Therefore, the change in the proportion of GNC was not compared in subsequent studies. 50 children with ADA were selected for the study, 26 and 24 of both sexes, respectively. The relationship between the effect of different gender and age on the intestinal flora of ADA children before and after taking antibiotics was compared, as displayed in **Figure 1**.

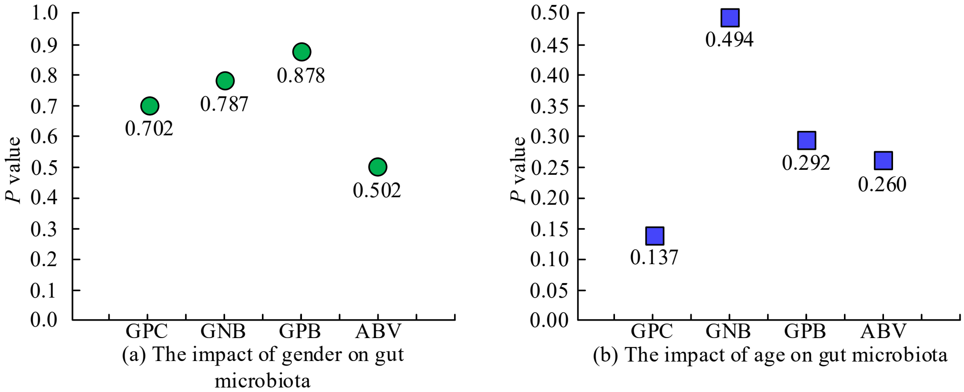

Figure 1. Comparison of the effects of gender and age on the gut microbiota of pediatric patients before and after taking antibiotics

In **Figure 1(a),** the *P* value of GPC, GNB, GPB, and ABV in the intestinal flora of both males and females was greater than 0.05, indicating that gender did not affect the changes in intestinal flora. In **Figure 1(b)**, the *P* values of intestinal flora of children of different ages were greater than 0.05, indicating that the differences were not statistically significant, thus indicating that age did not affect the changes in intestinal flora.

3.3. Analysis of other factors influencing intestinal flora in children with ADA and healthy children

The influencing factors of intestinal flora investigated in the study were duration of exclusive breastfeeding, mode of delivery, only child status, living environment, and probiotic and antibiotic use in children before the age of 1 year. A comparison of the percentage of the number of people in the different influencing factor groupings of ADA-affected and healthy children is shown in **Figure 2**.

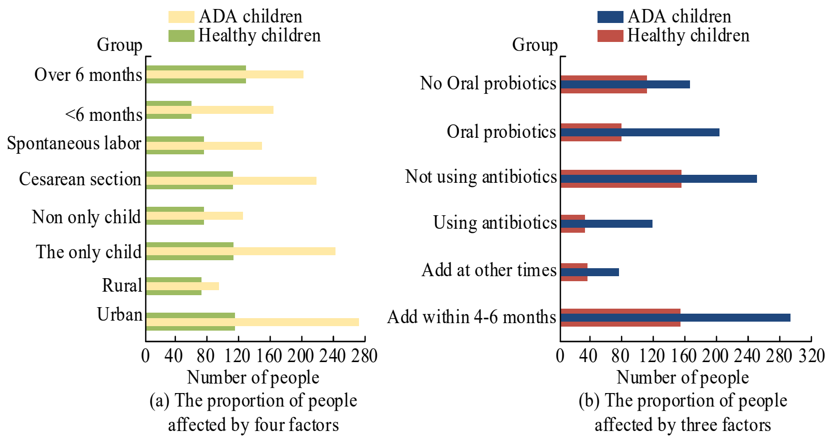

Figure 2. The proportion of people grouped by different influencing factors of ADA children and healthy children

In **Figure 2(a)**, the percentages of children with ADA and healthy children living in rural areas were 25.61% and 38.38%, and the percentages of children living in towns were 74.39% and 61.62%, respectively, $P = 0.002$ (< 0.05). The mode of delivery of the children with ADA and the healthy children was not statistically significant at $P = 0.927$ (> 0.05). The percentages of children with ADA and healthy children exclusively breastfed for more than 6 months were 55.31% and 69.19% and less than 6 months were 44.69% and 30.81% respectively, $P = 0.002$ (< 0.05). In **Figure 2(b)**, the percentages of ADA children and healthy children who had been exposed to antibiotics before 1 year of age were 31.88% and 16.76%, and the percentages of those who had not been exposed to antibiotics were 68.12% and 83.24%, respectively, $P = 0.000$ (< 0.05). The percentages of ADA children and healthy children who had been exposed to probiotics orally were 55.04% and 41.08%, respectively, and the percentages of not taking probiotics orally were 44.96% and 58.92%, respectively, $P = 0.002$ (< 0.05). Probiotics can promote the increase and dominance of beneficial bacteria by competitively crowding out and inhibiting the growth of harmful bacteria. These beneficial bacteria can help maintain the balance of intestinal flora, improve immune function, and contribute to the digestion and absorption of nutrients. At the same time, probiotics can enhance intestinal barrier function, prevent harmful substances and bacteria from entering the blood circulation and reduce intestinal allergic reactions. This is critical for the development of children's immune systems and the prevention of allergic diseases. The OR, 95% confidence interval, and *P* value of ADA-affected and healthy children are shown in **Figure 3**.

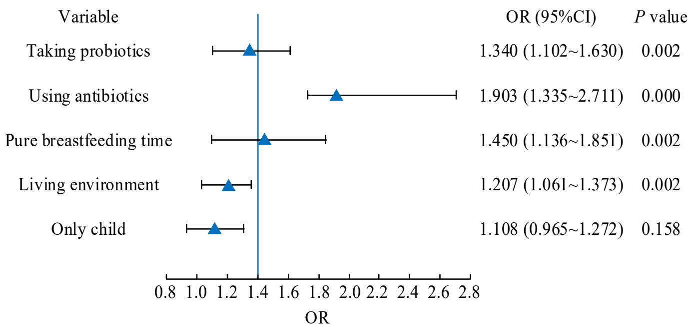

Figure 3. Correlation analysis of factors affecting intestinal flora between ADA children and healthy children

In **Figure 3**, comparing the ADA children and healthy children with or without only child status, $P = 0.158$ (> 0.05). The prevalence of ADA was higher in children with ADA who were exclusively breastfed for more than 6 months, lived in towns, took oral probiotics during infancy, and were exposed to antibiotics. Therefore, children with ADA were associated with their duration of exclusive breastfeeding, living environment, and probiotic and antibiotic use during infancy.

3.4. Factors influencing the targeting of asthma control in children with ADA

The study used one-way logistic regression to analyze the data of children with incomplete control and complete control of ADA, and the results are shown in **Figure 4**.

In **Figure 4**, the influencing factors of children with ADA against asthma control were age ($P = 0.001$), respiratory infection ($P = 0.048$), and history of rhinitis ($P = 0.004$), which were less than 0.05 and statistically significant. Since ADA is an allergic disease, dust mite allergy was also statistically significant, $P = 0.04$ (< 0.05). The factors influencing the level of asthma control in children with ADA were age, history of rhinitis, respiratory infection, and dust mite allergy. To further analyze the independent risk factors for asthma control in children with ADA, multifactorial logistic regression was chosen to study these four influencing factors, as presented in **Table 3**.

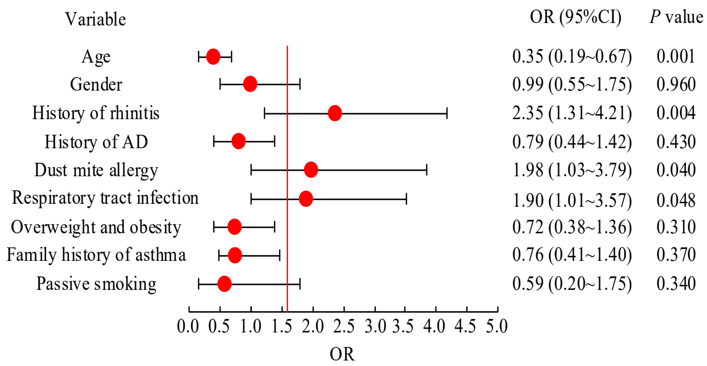

Figure 4. Univariate analysis of factors influencing the level of asthma control in ADA children

Table 3. Logistic regression analysis results of ADA disease-related risk factors

Variable	*β*	SE	Wals	Sig	OR	95% CI upper limit	95% CI lower limit
Age	-0.95	0.42	8.010	0.006	0.38	0.20	0.80
Dust mite allergy	0.70	0.89	0.490	0.460	2.01	0.31	12.03
History of rhinitis	0.91	0.39	6.500	0.011	2.29	1.19	4.39
Respiratory tract infection	0.10	0.90	0.019	0.890	1.15	0.19	6.50

Age ($P = 0.006$) and history of rhinitis ($P = 0.011$) were less than 0.05 and were statistically significant. While dust mite allergy, $P = 0.460$ (> 0.05) was not statistically significant. Therefore, the independent risk factors for asthma control were age and history of rhinitis.

3.5. Logistic regression analysis of risk factors in children with ADA

To further analyze the factors of ADA disease risk, binary logistic regression analyzed the duration of exclusive breastfeeding, living environment, and probiotic and antibiotic use in children before 1 year of age, and the results are shown in **Table 4**.

Table 4. Logistic regression analysis results of ADA disease-related risk factors

Variable	*β*	SE	Wals	Sig	Exp (B)	95% CI upper limit	95% CI lower limit
Urban life	0.602	0.201	8.709	0.004	1.800	1.223	2.703
Exclusive breastfeeding time < 6 months	0.499	0.200	6.622	0.009	1.666	1.099	2.398
No oral probiotics	-0.360	0.189	3.497	0.060	0.701	0.506	1.020
Using antibiotics	0.761	0.246	10.265	0.001	2.132	1.445	3.408
Constant	-3.002	0.564	28.001	0.000	0.053	/	/

According to Sig value, urban life ($P = 0.003$), exclusive breastfeeding less than 6 months ($P = 0.009$), and antibiotic use before 1 year of age ($P = 0.001$) were all < 0.05, which is statistically significant. Thus, risk factors for the development of ADA disease in children include living in a town, exclusive breastfeeding for less than 6 months, and use of antibiotics before 1 year of age.

4. Discussion

ADA is a common allergic disease in children, and the imbalance of intestinal flora is important for its pathogenesis. The pathogenesis of ADA is complex, including genetic, environmental, and immunologic factors [7]. Recent studies have increasingly demonstrated the significant role that intestinal flora plays in the occurrence and development of children with ADA. Several studies have proposed that the intestinal flora of children with ADA is significantly different compared to normal individuals [8]. For example, increased or decreased abundance of certain flora has been associated with the development of atopic dermatitis with asthma. Some of these studies suggest that an increase in specific flora may lead to overactivation of the immune system, which in turn triggers an allergic reaction [9]. Alternatively, imbalances in the flora may lead to impairment of the intestinal barrier function, making it easier for allergens to enter the body, thereby promoting atopic dermatitis and asthma [10]. The effect of antibiotic use on the intestinal flora is thought to be an important factor contributing to this imbalance. Normally, there is a balance of microbiome immunomodulation between the intestinal flora and the host's immune system. However, the broad-spectrum bactericidal effects of antibiotics may lead to the loss of beneficial bacteria as well as the overgrowth of harmful bacteria, upsetting the balance between the flora and the host. Therefore, the study compared the changes in the intestinal flora of children with ADA before and after treatment with antibiotics to explore the risk factors for morbidity in children. It also analyzed the differences between asthma-controlled children and healthy children and explored whether there is any correlation between the level of control and intestinal flora in asthmatic children, to further reveal the potential association between intestinal flora and atopic dermatitis with asthma.

In this study, the changes in intestinal flora before and after treatment with antibiotics were compared. It was found that the changes in the intestinal flora of children with ADA after the use of antibiotics were characterized by increasing the proportion of Gram-positive cocci and decreasing that of Gram-positive bacilli. In addition, intestinal flora imbalance in ADA patients taking antibiotics may be an important factor leading to the exacerbation of allergic symptoms. The broad-spectrum bactericidal effect of antibiotics may lead to the loss of beneficial bacteria and overgrowth of harmful bacteria, disrupting the balance between the flora and the host. In addition, the imbalance of intestinal flora may further affect the regulatory function of the immune system, leading to the occurrence of abnormal immune responses and increased inflammatory reactions. Therefore, it is important to further investigate the relationship between intestinal flora and ADA for the development of new therapeutic strategies and preventive measures. Comparing the P values of intestinal flora of patients of different genders and ages, the results were greater than 0.05, indicating that the differences were not statistically significant, and therefore gender and age did not affect the changes in intestinal flora. Kielenniva *et al.* analyzed the bacterial composition of the first meconium by sequencing bacterial 16S rRNA gene amplicons and found no evidence to confirm the relationship between the atopic manifestations of the disease in patients less than 4 years of age and the first meconium gut microbiota composition [11]. The etiology of ADA is not fully understood, but it has been shown that abnormal immune system response and genetic factors are important for its development. In this study, the percentages of ADA-affected and healthy children living in rural areas were 25.61% and 38.38% respectively, and the percentage living in towns were 74.39% and 61.62% respectively, $P = 0.002$ (< 0.05). When Mahdavinia *et al.* compared the children with and without AD, they found significant differences in bacterial composition and diversity. In addition, there was a significant difference in house dust microbiota between rural and urban areas [12]. However, some studies have stated that prenatal, gestational, or neonatal use of antibiotics may adversely affect the neonatal gut microbiome and negatively impact the development of the infant immune system, leading to ADA disorders in children [13]. Maternal mode of delivery in children with ADA and healthy children, $P = 0.927$ (> 0.05), was not statistically significant. Lee-Sarwar *et* *al.* conducted a study and concluded that there is no direct relationship between mode of delivery and asthma, but confirmed that cesarean delivery reduces fecal bacillus-like organisms and microbial sphingolipids and increases susceptibility to early asthma [14].

In addition, certain studies have suggested that the intestinal flora of children with ADA is influenced by a variety of factors. Levan *et al.* have suggested that disruption of the gut microbiome in early life is associated with ADA disease in childhood [15]. Sasaki compared fecal microbiota composition, abundance of selected flora, and fermentation metabolites, and found that degrading bacteria may play an important role in the differences in microbial cross-feeding between children with and without AD and the metabolite formation differences [16]. The influences of age (P = 0.001), respiratory infection (P = 0.048), and history of rhinitis (P = 0.004) among the factors targeting asthma control in children with ADA were less than 0.05 and statistically significant. Since ADA is an allergic disease, dust mite allergy also plays a significant role (P = 0.04). The factors influencing the level of asthma control in children with ADA are age, history of rhinitis, respiratory infection, and dust mite allergy. Some experts found that probiotics were effective in AD after the age of 1 year and there was no significant difference in the prevention of asthma, rhinitis, wheezing, allergic diseases, and sensation [17]. Before the age of 1 year, 31.88% and 16.76% of ADA children and healthy children were exposed to antibiotics, and 68.12% and 83.24% were not exposed to antibiotics, respectively, with P = 0.000. The percentages of ADA children and healthy children who took probiotics orally were 55.04% and 41.08%, and the percentages of those who did not take oral probiotics were 44.96% and 58.92% respectively (P = 0.002). Some studies have analyzed factors such as cesarean section and use of antibiotics before the age of 3 years, with an imbalance in the intestinal microbiota, which has been associated with a higher risk of developing allergic diseases in the future [18,19]. The results confirmed that the risk factors that predispose children to ADA diseases are the use of antibiotics before the age of 1 year, and the prevention of ADA diseases in children measures postnatal exclusive breastfeeding until the age of 6 months. Firstly, changes in the early life environment, such as mode of delivery, feeding practices, and antibiotic use, may have a long-term effect on the composition of the intestinal flora [20]. Secondly, changes in dietary composition, such as high-fat diets and lack of dietary fiber, may also affect the balance of intestinal flora [21]. In addition, environmental pollution, drug use, and psychological factors may also have an impact on the intestinal flora.

5. Conclusion

In summary, antibiotic use is associated with morbidity in children with ADA, and the use of antibiotics leads to changes in the intestinal flora. The number of Gram-positive cocci increases and the number of Gram-positive bacilli decreases after antibiotic use. In addition, a risk factor for ADA susceptibility in children is the use of antibiotics before the age of 1 year. This may be due to the close correlation between the development of intestinal flora and the maturation of the immune system during infancy and early childhood. Antibiotic use may disrupt the normal balance of intestinal flora, which in turn affects the development and regulation of the immune system and increases the risk of atopic dermatitis and asthma. However, the sample size may be limited, and the diversity and size of the samples may not be sufficient to fully assess the relationship between intestinal flora and ADA, which could be improved in the future.

Disclosure statement

The authors declare no conflict of interest.

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