Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Correlation between immunoglobulin index level and disease severity and clinical manifestations in children with atopic dermatitis as a chronic inflammatory

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ARTICLE INFO

Original paper

Article history:
Received: July 17, 2023
Accepted: November 12, 2023
Published: December 31, 2023

Keywords:

atopic dermatitis (AD) in children, immunoglobulin, IgE, severity of illness; skin dryness, chronic inflammatory

ABSTRACT

It was to analyze the clinical characteristics of atopic dermatitis (AD) in children and its relationship with immunoglobulin (IgG, IgA, IgM, IgE) levels. 400 children with AD in the dermatology clinic of Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital(SCMC-FMU) were the study subjects, and 200 normal children were enrolled as the blank control. The clinical data of the included children were collected, and the serum immunoglobulin levels and other related indicators were measured. The results showed that the IgE level was higher observably in group A when we compared it with group A0, the IgE level was much higher in group B in comparison to group B0, group C showed higher IgE level C than in group C0, and it was the same case in groups D and D0($P < 0.05$). The IgM level was decreased greatly in group C than that in normal children in group C0 ($P < 0.05$), but showed no visible difference among other groups ($P > 0.05$). The O-SCORAD scores of groups A, B, C, and D were significantly positively correlated with IgE level ($P < 0.05$). No great correlation was observed between skin dryness and IgE-specific allergen, IgG, IgA, IgM, and IgE levels in groups A - D ($P > 0.05$). Immunoglobulin deficiency was present in AD children compared with normal children, and IgE could be used as an efficient indicator to assess the severity of AD in children.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.15.2

Introduction

Atopic dermatitis (AD), as an inflammation, occurs in the upper layer of human skin and is characterized by long-term chronic itching. The incidence of AD is higher in patients with hay fever or asthma and their family members (1). The prevalence of AD is higher in urban areas or developed countries than in urban areas or underdeveloped countries, and it is more common in children or adolescents (20%) than in adults (1% to 3%). 60% of AD cases in infancy present in the first year of life, usually in the second or third month of life, and some in the second or third week of life (2-5). AD that develops during childhood often disappears or decreases in adulthood. Many factors can worsen AD (6,7). The rash mainly occurs on the cheeks, forehead, and scalp, and may progress to the trunk and limbs in some cases. The site of rash is often the site where the child can grasp and rub, which is mainly manifested as erythema, papules, bullous eruptions, blisters, exudates, and other changes on the face, scalp, neck, and trunk, and pustules may occur in secondary infection (8). Lesions in childhood, decreased exudation, and pruritus was constant feature, and therefore, most of the rash changes are secondary to pruritus. Scratching leads to lichenification of skin lesions and secondary infection mainly manifested as chronic dermatitis lesions such as antecubital fossa, popliteal fossa, ankle, dorsum of foot, dryness behind the ears, and hypertrophic leatherization, because it often occurs on the flexural side of the joints of the extremities, also known as ectopic eczema; if AD develops after the age of 2 years, it often has a long course of the disease and is refractory.

Many people who have AD or their families also have allergic reactions (asthma and/or immediate hypersensitivity reactions), manifested as, allergic seasonal or perennial rhinoconjunctivitis (9,10). In addition to the above skin features, allergic skin diseases are also manifested as dryness, excessive palm wrinkles, keratosis hair processes, suborbital skin folds, lateral eyebrow thinning, hair intolerance, white skin, and increased transdermal water loss (in unaffected and affected skin) (11). The genes associated with AD encode epidermal and immune proteins. In terms of genes, many people can't fully perform the function of the filaggrin coding gene or have gene mutations, making them susceptible to AD (12,13). As keratinocytes differentiate, they produce keratinocytes, an important component of the cell envelope known as filaggrin. Ultimately, it is essential to establish a moisture barrier that protects the cuticle. Filaggrin insufficiency or functional variation is present in approximately one in ten European populations, which increases the risk of elevated IgE levels and, in turn, increases the incidence of more severe AD (14). Currently, there are no techniques to cure or prevent AD, mainly through the use of corticosteroids, calcineurin inhibitors, antihistamines, and other drug interventions, but it can only relieve symptoms and will cause various adverse reactions

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and drug resistance (15,16). In this view, it is necessary to investigate the clinical characteristics of children with AD to seek treatment options. Therefore, 400 children with AD who were diagnosed and treated in the dermatology clinic of Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital(SCMC-FMU) were included as the study subjects, and 200 normal children who were examined contemporaneously were included as the blank control. Clinical data of the included children were collected, and the serum immunoglobulin levels and other related indicators of the children were measured. Spearsman was used to analyze the relationship between immunoglobulin indicators and the severity of AD, and the clinical characteristics of AD in children and the relationship with immunoglobulin (IgG, IgA, IgM, IgE) levels were deeply analyzed.

Materials and Methods

Study participants

From October 10, 2016 to October 15, 2022, 400 children with AD who were diagnosed and treated in the Dermatology Clinic of Shanghai Medical College were selected as the research objects, and 200 normal children who underwent physical examination during the same period were selected as the blank control. After being reviewed by the hospital ethics committee, this clinical trial was approved and executed, and all patients voluntarily participated and signed the informed consent.

Inclusion criteria of children with AD were described to obey the following items: (i) children aged under 3 years old; (ii) no relevant treatment in the past month; (iii) no secondary severe infection; (iv) complete collection of clinical data. Exclusion criteria: (i) children with immunodeficiency disease; (ii) children with other allergic diseases; (iii) children with good treatment compliance.

Inclusion criteria of normal children were presented as follows: (i) children aged under 3 years old; (ii) no previous use of glucocorticoids or other immunosuppressive agents for one month; (iii) no previous use of antihistamines for half a month; Exclusion criteria: (i) children with infectious diseases; (ii) children with recent poisoning; (iii) children with missing baseline data; (iv) children with other blood system diseases.

Grouping criteria

According to the changes of transient hypogammaglobulinemia of infancy (THI), 400 children with AD were divided into 4 groups: 158 cases in group A (0-6 months), 95 cases in group B (7-12 months), 94 cases in group C (13-36 months), and 53 cases in group D (36-72 months). 200 normal children were also divided into 83 cases in group A0 (0-6 months), 52 in group B0 (7-12 months), 50 in group C0 (13-36 months), and 15 in group D0 (36-72 months).

Clinical data

Age, sex, past medical history, genetic history, skin lesion area, skin disease type, and objective scoring atopic dermatitis index (O-SCORAD) were recorded for all children.

Venous blood samples were collected from the included children, and immunoglobulin IgA, IgM, and IgG levels were measured by immunoturbidimetry in children. Immunoglobulin IgE levels in children were measured by chemiluminescence. Immunoglobulin IgE-specific allergens in children were detected by immunoblotting.

Statistical analysis

Data were processed and analyzed using SPSS 19.0, measurement data were displayed in the form of mean ± standard deviation ($\bar{x}\pm s$), and enumeration data were given as a percentage (%). The *t*-test and log-rank test were used to analyze the differences in data between the groups. Spearsman was used to detect the association between gender, age, past medical history, genetic disease history and immunoglobulin IgA, IgM, IgG, IgE, and IgE-specific allergens. Two-sided tests were statistically significant at $P < 0.05$.

Results

Gender comparison between AD children and normal children at different ages

As shown in Figure 1, 102, 61, 55, and 30 males and 56, 34, 39, and 23 females were enrolled in groups A – D, respectively. In groups A0 – D0, the numbers of male and female participants were 43, 35, 31, and 11 vs 40, 17, 19, and 4, respectively. The number of men and women between children in group A and normal children in group A0 showed an obvious difference ($P < 0.05$). No remarkable difference in the number of males was observed between group B and normal children in group B0, between group C and normal children in group C0, or between group D and normal children in group D0 ($P > 0.05$).

Immunoglobulin levels between AD children and normal children at different ages

Children in group A had IgG levels of 3.295 ± 1.055 g/L, IgA levels of 0.207 ± 0.044 g/L, IgM levels of 0.391 ± 0.141 g/L, and IgE levels of 91.178 ± 33.274 g/L; children in group A0 had IgG levels of 3.482 ± 1.133 g/L, IgA levels of 0.185 ± 0.072 g/L, IgM levels of 0.426 ± 0.135 g/L, and IgE levels of 22.618 ± 10.093 g/L. The IgG, IgA, and

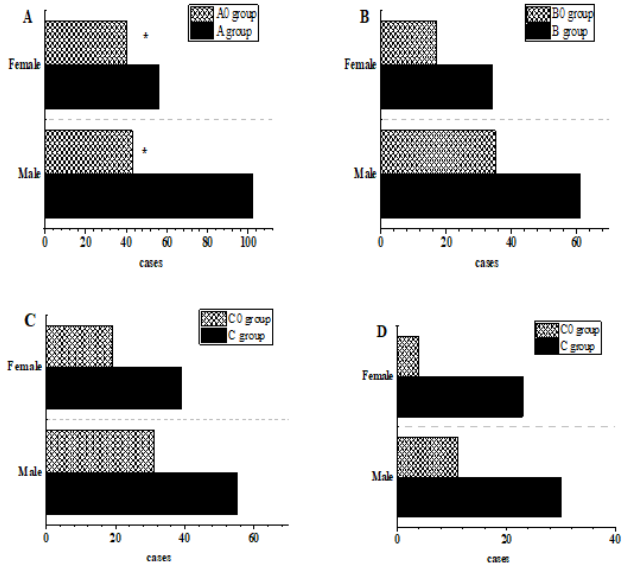

Figure 1. Gender comparison between AD children and normal children at different ages. (A, B, C, and D showed the children in groups A and A0, groups B and B0, groups C and C0, and groups D and D0, respectively). Note: * indicated $P<0.05$.

IgM levels between group A and normal children in group A0 differed not greatly ($P > 0.05$); IgE levels in group A were observed to be higher than those in normal children in group A0 ($P < 0.05$) (Figure 2).

Children in group B had IgG levels of 4.475 ± 1.409 g/L, IgA levels of 0.183 ± 0.052 g/L, IgM levels of 0.671 ± 0.125 g/L, and IgE levels of 142.215 ± 35.072 g/L; children in group B0 had IgG levels of 4.426 ± 1.382 g/L, IgA levels of 0.205 ± 0.077 g/L, IgM levels of 0.695 ± 0.143 g/L, and IgE levels of 39.828 ± 11.473 g/L. We found the differences were not noticeable in IgG, IgA, and IgM levels between group B and normal children in group B0 ($P > 0.05$); and IgE levels in group B were significantly higher than those in normal children in group B0 ($P < 0.05$) (Figure 3).

In group C, IgG level was 6.183 ± 1.552 g/L, IgA level was 0.571 ± 1.143 g/L, IgM level was 0.922 ± 0.403 g/L, and IgE level was 159.338 ± 50.063 g/L; in group C0, IgG level was 6.405 ± 1.416 g/L, IgA level was 0.488 ± 0.135 g/L, IgM level was 1.348 ± 0.389 g/L, and IgE level was 51.128 ± 18.053 g/L. The differences in IgG and IgA levels between group C and normal children in group C0 were found to be not great ($P > 0.05$); IgE levels in group C were observed to be elevated compared to the normal children in group C0, and IgM levels in group C were shown to be lower while those in normal children in group C0 were higher, showing($P < 0.05$) (Figure 4).

In group D, IgG level was 8.551 ± 1.672 g/L, IgA level was 0.955 ± 0.219 g/L, IgM level was 1.143 ± 0.365 g/L, and IgE level was 204.86 ± 71.13 g/L; in group D0, IgG level was 8.144 ± 1.583 g/L, IgA level was 0.898 ± 0.104 g/L, IgM level was 1.066 ± 0.322 g/L, and IgE level was 65.172 ± 14.368 g/L. The IgG, IgA, and IgM levels between group D and normal children in group D0 differed slightly, without any significance ($P > 0.05$); IgE levels in group D were higher than those in normal children in group D0 ($P < 0.05$) (Figure 5).

Relationship between immune protein parameters and family history of allergic diseases in AD children of different ages

As shown in Table 1, the family history of allergic diseases in group B was significantly correlated with the number of IgE-specific allergens ($r = 0.294$, $P = 0.011$), but not with IgG, IgA, IgM, or IgE levels ($P > 0.05$). The correlation of the family history of allergic diseases to the number of IgE-specific allergens, IgG, IgA, IgM, and IgE levels showed P > 0.05 in groups A, C, and D.

Relationship between immune protein parameters and dry skin in AD children of different ages

As shown in Table 2, the correlation of skin dryness to the number of IgE-specific allergens, IgG, IgA, IgM, and IgE levels in children was not obvious enough in groups A - D ($P > 0.05$).

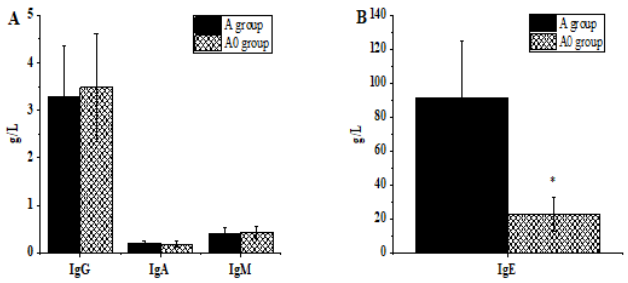

Figure 2. Immunoglobulin levels comparison between AD children aged 0-6 months and normal children (A for IgG, IgA, IgM; B for IgE). Note: * indicated$P < 0.05$.

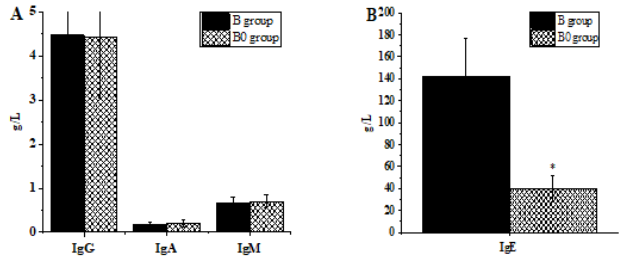

Figure 3. Immunoglobulin levels comparison between AD children aged 7-12 months and normal children (A for IgG, IgA, IgM; B for IgE). Note: *: $P < 0.05$.

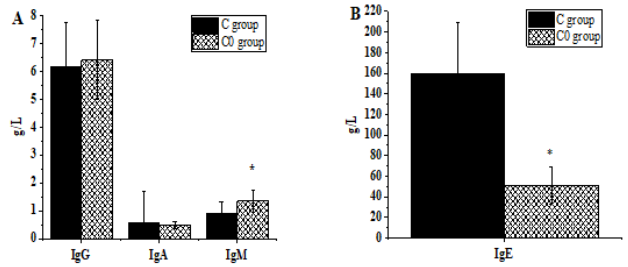

Figure 4. Comparison of immunoglobulin levels between AD children aged 13-36 months and normal children. (A for IgG, IgA, IgM; B for IgE). Note: * marked $P < 0.05$.

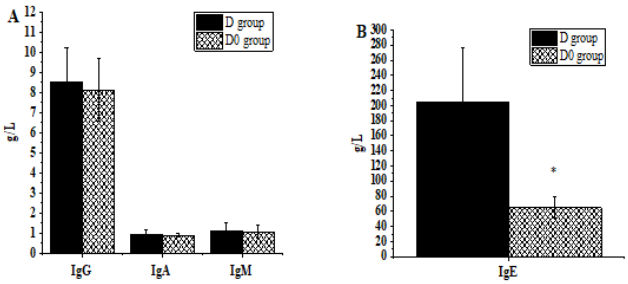

Figure 5. Immunoglobulin levels comparison between AD children aged 36-72 months and normal children. (A for IgG, IgA, IgM, B for IgE). Note: * suggested $P < 0.05$.

Table 1. Relationship between immune protein parameters and family history of allergic diseases in AD children of different ages.

r (P)	IgG	IgA	IgM	IgE	IgE-specific allergen
Group A	0.158 (0.072)	0.089 (0.115)	-0.075 (0.093)	0.015 (0.058)	-0.098 (0.062)
Group B	0.152 (0.056)	-0.165 (0.051)	-0.124 (0.088)	0.237 (0.072)	0.294 (0.011)
Group C	0.084 (0.129)	0.104 (0.083)	0.004 (0.058)	-0.105 (0.087)	0.044 (0.061)
Group D	0.158 (0.072)	0.017 (0.068)	0.123 (0.155)	0.118 (0.142)	-0.026 (0.081)

Table 2. Relationship between immune protein parameters and dry skin in AD children of different ages.

r (P)	IgG	IgA	IgM	IgE	IgE-specific allergen
Group A	0.174 (0.078)	0.073 (0.108)	-0.091 (0.115)	0.017 (0.063)	0.054 (0.066)
Group B	0.118 (0.052)	0.152 (0.071)	-0.145 (0.087)	0.273 (0.091)	0.354 (0.061)
Group C	0.085 (0.113)	0.144 (0.063)	0.022 (0.078)	-0.128 (0.077)	0.044 (0.061)
Group D	0.171 (0.060)	0.007 (0.067)	0.113 (0.148)	0.123 (0.139)	-0.041 (0.054)

Table 3. Relationship of immune protein parameters to O-SCORAD score in AD children aged different months

r (P)	IgG	IgA	IgM	IgE	IgE-specific allergen
Group A	0.106 (0.099)	-0.061 (0.131)	0.028 (0.102)	0.173 (0.021)	0.216 (0.014)
Group B	0.082 (0.104)	-0.227 (0.000)	-0.067 (0.053)	0.187 (0.069)	0.278 (0.081)
Group C	0.019 (0.021)	-0.071 (0.055)	0.346 (0.000)	0.371 (0.000)	0.312 (0.009)
Group D	0.182 (0.073)	0.022 (0.097)	0.134 (0.102)	0.118 (0.064)	0.288 (0.012)

Relationship between immune protein parameters and O-SCORAD scores in AD children aged different months

The O-SCORAD score of children in group A was significantly positively correlated with IgE levels ($r = 0.173$, $P = 0.021$) and the number of IgE-specific allergens (r = 0.216, $P = 0.014$), but not significantly correlated with IgG, IgA, and IgM levels ($P > 0.05$). A negative correlation was demonstrated between O-SCORAD score and IgA level ($r = -0.227$, $P = 0.000$), but correlation demonstrated no significance between O-SCORAD score and IgG, IgM, IgE level, or the number of IgE-specific allergens in group B ($P > 0.05$). O-SCORAD scores in group C were positively related to IgM levels ($r = 0.346$, $P = 0.000$), IgE levels ($r = 0.371$, $P = 0.000$), and the number of IgE-specific allergens ($r = 0.312$, $P = 0.009$), but not with IgG or IgA levels ($P > 0.05$). We observed an extremely positive correlation between the O-SCORAD score and the number of IgE-specific allergens in group D ($r = -0.288$, $P = 0.012$), while it was the opposite case for a correlation between the O-SCORAD score and IgG, IgA, IgM, and IgE levels ($P > 0.05$). The above contents could be observed in Table 3.

Discussion

AD is a genetically predisposed allergic skin disease that is a chronic inflammatory, pruritic, and recurrent; it is common in children and can also be observed in adults; it is often accompanied by elevated IgE and a personal or family history of the atopic disease (17). AD patients have more than eczema, and allergic rhinitis and allergic asthma generally develop as the disease progresses (18). AD can affect the patients' quality of life extremely greatly, so cognitive understanding of the disease is of great research value (19-21). 400 children with AD who were diagnosed and treated in the dermatology clinic of SCMC-FMU from October 10, 2016, to October 15, 2022, were included as the study subjects, while 200 normal children for physical examination contemporaneously were included as the blank control. Clinical data of the included children were collected, and the serum immunoglobulin levels and other related indicators of the children were measured. There was a significant difference in the number of males and females between group A and group A0 ($P < 0.05$), but no remarkable difference was demonstrated in the number of males between group B and group B0, group C and group C0, and group D and group D0 ($P < 0.05$), which suggests that although there was a difference in the number of boys and girls at 0-6 months of age, age as a whole can't be used as an indicator to assess the condition of AD.

From the immunoglobulin levels, the IgE levels of children in groups A – D were significantly higher than those of normal children in groups A0 - D0 ($P < 0.05$). IgE is an antibody in the human body that is present in the blood and is the least IgE in the serum of normal subjects and can cause type I hypersensitivity, and more IgE indicates more severe allergy (22,23). The results suggest that IgE levels should be reexamined in children with AD, and complementary foods should be added to observe the changes in skin lesions in children. In addition, IgM levels in group C were lower than those in normal children in group C0, with $P < 0.05$, but $P>0.05$ was found in IgM levels in other groups ($P > 0.05$), indicating that IgM levels in AD children and normal children were only different at 12-36 months of age, which was different from the findings of Warshaw et al. (2021) (24). The reason for the analysis may be related to the intentional avoidance of food and attention to improving the living environment of family members of AD children after the addition of complementary foods (25). In order to further investigate the relationship between immunoglobulins and AD, Spearsman was used for analysis. First, it was found that there were no significant correlations between the family history of allergic diseases and IgG, IgA, IgM, and IgE levels in children in groups A - D ($P > 0.05$), which suggested that the family history of allergic diseases was not associated with immunoglobulin levels (26). In addition, the O-SCORAD scores of children in groups A, B, C, and D were significantly positively correlated with IgE levels ($P < 0.05$), which further suggests that IgE can be used as an efficient indicator to assess the severity of AD in children. IgG, IgA, and IgM levels were only associated with O-SCORAD scores in a single group of children, which suggests that the severity of AD in children is less associated with IgG, IgA, and IgM levels and they can't be used as an effective evaluation index.

Fundings

The research is supported by: the General Program of Fujian Natural Science Foundation (No. 2021J01356).

400 children with AD who were diagnosed and treated in the dermatology clinic of SCMC-FMU from October 10, 2016, to October 15, 2022, were included as the study subjects, while 200 normal children who were for physi-

cal examination contemporaneously were included as the blank control. The clinical data of the included children were collected, and the serum immunoglobulin levels and other related indicators of the children were measured. Spearsman was used to analyze the relationship between immunoglobulin indicators and the severity of AD. Finally, it was found that there was immunoglobulin deficiency in children with AD compared with normal children, and IgE could be used as an efficient indicator to assess the severity of AD in children. However, the enrolled study samples were collected from one hospital only, there may be geographical limitations, and the clinical data of the children were less analyzed, and the possible relationship between more baseline data and the child's condition was not explored. Therefore, the samples of the children from more sources will be re-included later to deeply analyze the indicative significance of serum immunoglobulin levels in AD. In summary, this result provides theoretical support for the diagnosis and treatment of AD in children.

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