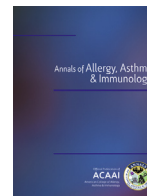




Contents lists available at ScienceDirect



Relationship between hypogammaglobulinemia and severity of atopic dermatitis

Mehmet Halil Celiksoy, MD^{*}; Erdem Topal, MD[†]; Recep Sancak, MD^{*}; Ferhat Catal, MD[†]; and Ayhan Sogut, MD^{*}

^{*} Department of Pediatric Allergy and Immunology, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

[†] Department of Pediatric Allergy and Immunology, Medical Faculty, Inonu University, Malatya, Turkey

ARTICLE INFO

Article history:

Received for publication April 15, 2014.

Received in revised form June 21, 2014.

Accepted for publication June 25, 2014.

ABSTRACT

Background: Atopic dermatitis is an itchy, inflammatory, chronic, or chronically relapsing skin disease. The disease occurs in people who have an “atopic tendency” or may appear as a clinical sign of primary immunodeficiency.

Objectives: To determine the relation between severity of atopic dermatitis and hypogammaglobulinemia.

Methods: One hundred sixty pediatric patients with atopic dermatitis (98 boys and 62 girls, 1–60 months old, median age 14.5 months) and 95 healthy children (57 boys and 38 girls, median age 16 months; control group) were included in the study. In patients with atopic dermatitis, the severity of disease was determined by the SCORing Atopic Dermatitis index. Serum immunoglobulin levels of all patients and children in the control group were measured by nephelometry on admission.

Results: The incidence of hypogammaglobulinemia was higher in patients with atopic dermatitis than in the control group ($P = .009$). The main reason for this difference was the low level of IgG in the atopic dermatitis group ($P = .024$). Analysis of the relation between hypogammaglobulinemia and the severity of atopic dermatitis showed no statistically significant difference between the group with mild to moderate atopic dermatitis and the group with severe atopic dermatitis with respect to hypogammaglobulinemia ($P = .859$), IgG ($P = .068$), IgA ($P = .410$), and IgM ($P = .776$) values.

Conclusion: Hypogammaglobulinemia was more frequent in patients with atopic dermatitis compared with the control group, mostly owing to the low IgG level. Hypogammaglobulinemia is not associated with the severity of atopic dermatitis.

© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Hypogammaglobulinemia is defined as low levels of at least 1 immunoglobulin isotype less than 2 SD of the mean value for age.¹ Some children with hypogammaglobulinemia achieve normal immunoglobulin levels in early life stages and these patients are defined as having transient hypogammaglobulinemia of infancy. In other individuals, hypogammaglobulinemia can occur in middle childhood or early adulthood. Atopic diseases are common in transient hypogammaglobulinemia and primary immunodeficiencies owing to antibody deficiency.² The skin is an organ with an active immune system that indicates systemic immunity.³ Atopic dermatitis is common in some primary immunodeficiencies, such as selective IgA deficiency, common variable immunodeficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, hyper-IgE syndrome, and Omenn syndrome.⁴

Reprints: Mehmet Halil Celiksoy, MD, Department of Pediatric Allergy and Immunology, Medical Faculty, Ondokuz Mayıs University, 55139 Kurupelit, Samsun, Turkey; E-mail: drmh@hotmai.com.

Disclosure: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2014.06.025>

1081-1206/© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

The aims of this study were to determine the relation between atopic dermatitis and hypogammaglobulinemia and to investigate the effect of hypogammaglobulinemia on the severity of atopic dermatitis.

Methods

This prospective study was conducted in the Department of Pediatric Allergy and Immunology of the Medical Faculty of Ondokuz Mayıs University and İnönü University from March 2013 through March 2014.

Study Group

One hundred sixty pediatric patients with atopic dermatitis (1–60 months old) and 95 healthy children (control group) were included in the study. The diagnosis of atopic dermatitis was established according to the criteria of Hanifin and Rajka.⁵ All patients had chronic or chronically relapsing dermatitis, pruritus, and typical morphology and distribution (facial and extensor involvement). Demographic data, such as age of onset of atopic

dermatitis, regular breast milk intake, exposure to tobacco smoke, accompanying atopic disease, and family history of atopy, were queried. Patients older than 6 months underwent skin prick testing. Serum IgG, IgA, and IgM concentrations, allergen-specific IgE, total serum IgE, and peripheral eosinophilia values of all patients were measured at admission. The severity of atopic dermatitis was determined using the SCORing Atopic Dermatitis (SCORAD) index. Patients with a SCORAD score below 25 were classified as having mild atopic dermatitis, those with a score from 25 to 50 were classified as having moderate atopic dermatitis, and those with a score above 50 were classified as having severe atopic dermatitis. The maximum SCORAD score was 103.^{6,7} Patients receiving systemic or topical corticosteroids in past 3 months were excluded from the study.

Definition of Hypogammaglobulinemia

The inclusion criterion consisted of decreased serum levels of at least 1 major immunoglobulin isotype at presentation, defined as at least 2 SD below the age-defined norms in Turkish healthy children.⁸ Patients with primary immunodeficiency accompanied by atopic dermatitis and those receiving drugs (eg, corticosteroids, angiotensin-converting enzyme inhibitors, or antiepileptic drugs) that can lead to hypogammaglobulinemia were excluded from the study.⁹

Laboratory Studies

Total serum Ig levels were measured by nephelometry using commercially available kits. Total IgE and allergen-specific IgE were measured using capture enzyme-linked immunosorbent assay and radioallergosorbent test, respectively. The count and percentage of peripheral blood eosinophils were determined. Skin prick tests were performed on the volar aspect of the forearm for foods (cow's milk, egg white, and wheat) and common aeroallergens (house dust mites, cockroaches, animal dander, mold, and mixed grass pollen). The reaction was read 15 minutes later. The test result was considered positive if the diameter of the wheal was at least 3 mm larger than that of the negative control. Patients with at least 1 positive skin prick test reaction or specific IgE positivity were defined as sensitized, and those who did not have any positive result were defined as not sensitized.

Statistics

Statistical analysis was performed using SPSS 17.0 (SPSS, Inc, Chicago, Illinois). Descriptive statistics were expressed as frequency and percentage for categorical variables, whereas quantitative data were expressed as median for non-normally distributed data. The Mann-Whitney *U* test was used to compare 2 groups (atopic eczema group and healthy control group), and the χ^2 test was used to compare the categorical variables.

Ethical Considerations

The study was approved by the ethics committee of the Medical Faculty of Ondokuz Mayıs University. Written informed consent was obtained from the parents of all participants.

Results

The study included 160 patients who were diagnosed with atopic dermatitis (98 boys and 38 girls, median age 14.5 months) and 95 healthy children (57 boys and 38 girls, median age 16 months; control group). Patients with atopic dermatitis were categorized as having a mild to moderate form or a severe form. Comparison of these 2 groups showed that although atopic dermatitis was more severe in patients with an early onset of disease ($P = .006$), it was less severe in patients who were fed with

Table 1

Demographic data of patients and relation between hypogammaglobulinemia and severity of atopic dermatitis

	Mild to moderate eczema	Severe eczema	P value
Boys, n (%)	66 (61.1)	32 (61.5)	1.000
Age (mo), median (min–max)	18 (2–90)	11 (3–58)	.06 ^a
Age at first eczema episode (mo), median (min–max)	5.7 (1–120)	3 (1–62)	.124
Breastfeeding regularly, n (%)	87 (80.6)	33 (63.5)	.32 ^a
Tobacco exposure, n (%)	53 (49.1)	32 (61.5)	.190
History of atopic disease, in parents, n (%)	39 (36.1)	20 (38.5)	.909
Coexisting atopic disease, in patients, n (%)			
Recurrent wheezing	27 (25.0)	6 (11.5)	.078
Food allergy	15 (13.9)	8 (15.4)	.990
Drug allergy	5 (4.6)	0	.175
Skin prick test result, n (%)			
Aeroallergen sensitivity	29 (26.9)	11 (21.6)	.602
Food allergen sensitivity	29 (26.9)	26 (50.0)	.07 ^a
Peripheral eosinophilia, n (%)	57 (52.8)	30 (57.7)	.678
Serum immunoglobulin level, median (min–max)			
IgA (mg/dL)	36.9 (11–170)	28 (8–187)	.410
IgG (mg/dL)	698 (207–950)	586 (129–1,390)	.068
IgM (mg/dL)	73.5 (25–256)	68 (31–250)	.776
IgE (IU/L)	38 (8–1,900)	35 (2.8–1,630)	.743
Hypogammaglobulinemia (<2 SD), n (%)	18 (16.7)	10 (19.2)	.859

Abbreviation: min–max, minimum to maximum.

breast milk for at least 6 months ($P = .032$). No significant difference was observed between the severe and mild to moderate groups with respect to tobacco smoke exposure ($P = .190$), family history of atopy ($P = .909$), accompanying recurrent wheezing ($P = .078$), food allergy ($P = .990$), and drug allergy ($P = .175$). Evaluation of skin prick test results showed that although there was no significant difference between the severe and mild to moderate groups with respect to aeroallergen sensitivity ($P = .602$), the disease was more severe in patients with food sensitivity ($P = .007$). Peripheral eosinophilia ($P = .678$) and high levels of IgE ($P = .743$) had no influence on the severity of disease. No statistically significant difference was observed between the 2 groups for hypogammaglobulinemia ($P = .859$), IgG ($P = .068$), IgA ($P = .410$), and IgM ($P = .776$) values. Demographic characteristics of the patients who were diagnosed with atopic dermatitis are presented in Table 1.

Comparison of patients with atopic dermatitis with controls showed no significant difference with respect to age ($P = .175$). Hypogammaglobulinemia was more common in patients with atopic dermatitis than in controls ($P = .009$). The main reason for this difference was the low level of IgG in the atopic dermatitis group ($P = .024$). Conversely, there were no significant difference between the 2 groups with respect to IgA ($P = .189$) and IgM ($P = .069$) values (Table 2). Lymphocyte subsets of patients who had

Table 2

Hypogammaglobulinemia in relation to atopic dermatitis compared with control group

Variable	Atopic eczema group	Control group	P value
Age (mo), median (min–max)	14.5 (2–90)	16.0 (6–58)	.175
Serum immunoglobulin levels, n (%)			
IgA deficiency (<2 SD)	13 (8.1)	3 (3.2)	.189
IgG deficiency (<2 SD)	14 (8.8)	1 (1.1)	.024 ^a
IgM deficiency (<2 SD)	11 (6.9)	1 (1.1)	.069
Hypogammaglobulinemia (<2 SD), n (%)	28 (17.5)	5 (5.3)	.009 ^a

Abbreviation: min–max, minimum to maximum.

hypogammaglobulinemia were normal. The median IgE levels were 17 IU/L (2–121 IU/L) in the low-IgG group and 46.1 IU/L (1–1,900 IU/L) in the normal-IgG group ($P = .003$).

Discussion

To the best of the authors' knowledge, this study is the first in the literature demonstrating the effects of hypogammaglobulinemia on the severity of atopic dermatitis. The present study showed no relation between the severity of disease and hypogammaglobulinemia or low levels of IgG, IgA, and IgM in patients with atopic dermatitis. In addition, this study showed that the incidence of hypogammaglobulinemia was higher in patients with atopic dermatitis than in controls. IgG was the main cause of this difference and IgA and IgM values did not differ significantly between the 2 groups. These results suggest that there may be a relation between low IgG levels and atopic dermatitis. Serum IgG levels were significantly lower in patients with atopic dermatitis than in controls. Some patients with hypogammaglobulinemia had recurrent wheezing and infections. However, lymphocyte subsets of patients with hypogammaglobulinemia were normal. It should be noted that patients with the diagnosis of primary immunodeficiency were excluded from the present study. For the clinical significance of this finding, the correlation between the presence of atopic dermatitis and low serum IgG levels should be evaluated in patients with primary immune deficiency. In addition, children with atopic dermatitis should be considered for a differential diagnosis of primary immune deficiency regardless of disease severity. Furthermore, IgE level was higher in patients with normal IgG levels than in those with low IgG levels in this study. This condition may be due to the delay in the maturation of B cells.

Aside from hypogammaglobulinemia, other factors that can be associated with the severity of atopic dermatitis were examined in the study. In a cohort study examining the course of illness from birth until 7 years of age in children with atopic dermatitis, a young age was found to be the leading risk factor for persistent atopic dermatitis.¹⁰ Parental atopy was associated with a young age and severe atopic dermatitis.¹¹ A recent meta-analysis showed that the incidence of atopic dermatitis was lower in breastfed infants (for ≥ 4 months).¹² The association between exposure to secondhand tobacco smoke and atopic dermatitis has not been clearly determined.¹¹ In the present study, although atopic dermatitis was more severe in patients with early onset of disease, it was less severe in those receiving regular breast milk for at least 6 months. No significant association was observed between exposure to tobacco smoke and the severity of atopic dermatitis. These findings were consistent with those in the literature. However, in contrast with the literature, no association between family history of atopy and severity of atopic dermatitis was found.

Sensitization to food allergens (cow's milk and hen's eggs) is associated with infantile atopic dermatitis and severity of disease. Food allergen sensitization also is predictive for persistence of symptoms throughout childhood.¹⁰ In a study conducted in 1998, approximately one third of children with moderate to severe persistent atopic dermatitis had IgE-mediated food allergy.¹³ In the present study, the disease was more severe in patients with positive food skin test reactions and this finding was consistent with the literature. However, there was no significant relation between the presence of food allergy and the severity of disease. The difference

is due to the fact that the prevalence of food allergy was based only on medical history at admission. Large-scale cohort studies are needed to investigate the association between the presence of food allergy and the severity of atopic dermatitis. Although the great majority of children with atopic dermatitis are sensitive to at least 1 aeroallergen, the association between exposure to aeroallergens and atopic dermatitis is unknown. No clear evidence for the relation between early exposure to aeroallergens and increased risk for atopic dermatitis has been found.¹⁴ In the present study, no association between aeroallergen sensitivity and severity of atopic dermatitis at the skin test was found.

The study is important because it shows that hypogammaglobulinemia was not associated with the severity of atopic dermatitis, the incidence of hypogammaglobulinemia was higher, and IgG levels were significantly lower in patients with atopic dermatitis than in healthy children. The limitations of this study are that serum immunoglobulins were measured only at admission and IgG subclasses were not studied.

In conclusion, hypogammaglobulinemia (due to IgG deficiency) was more common in patients with atopic dermatitis than in healthy children. Clinically, primary immune deficiencies should be eliminated in patients presenting with atopic dermatitis regardless of severity. Because patients with primary immunodeficiency are often diagnosed late, the presence of atopic dermatitis can be an early warning sign for primary immunodeficiency.

References

- [1] Simonte SJ, Cunningham-Rundles C. Update on primary immunodeficiency: defects of lymphocytes. *Clin Immunol*. 2003;109:109–118.
- [2] Ozen A, Baris S, Aydinler EK, et al. Outcome of hypogammaglobulinemia in children: immunoglobulin levels as predictors. *Clin Immunol*. 2010;137:374–383.
- [3] Egawa G, Kabashima K. Skin as a peripheral lymphoid organ: revisiting the concept of skin-associated lymphoid tissues. *J Invest Dermatol*. 2011;131:2178–2185.
- [4] Aghamohammadi A, Gholizadeh Z, Moghaddam H, et al. Investigation of underlying primary immunodeficiencies in patients with severe atopic dermatitis [published online ahead of print June 1, 2013]. *Allergol Immunopathol (Madr)*. pii:S0301-0546(13) 00104–3.
- [5] Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol*. 1980;92:44–47.
- [6] Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186:23–31.
- [7] Oranje AP, Glazenburg EJ, Wolkerstorfer A, et al. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol*. 2007;157:645–648.
- [8] Aksu G, Genel F, Koturoglu G, Kurugöl Z, Kütükçüler N. Serum immunoglobulin (IgG, IgM, IgA) and IgG subclass concentrations in healthy children: a study using nephelometric technique. *Turk J Pediatr*. 2006;48:19–24.
- [9] European Society for Immunodeficiencies. Drug induced hypogammaglobulinemia. <http://esid.org/Working-Parties/Clinical/Resources/Diagnostic-criteria-for-PID2#Q3>. Accessed October 7, 2014.
- [10] Illi S, von ME, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol*. 2004;113:925–931.
- [11] Akdis CA, Akdis M, Bieber T, et al; European Academy of Allergy and Clinical Immunology/American Academy of Allergy; Asthma and Immunology. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol*. 2006;118:152–169.
- [12] Schafer T. [Prevention of atopic eczema. Evidence based guidelines]. *Hautarzt*. 2005;56:232–240.
- [13] Eigenmann PA, Sicherer SH, Borkowski TA, et al. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998;101:E8.
- [14] de Bruin Weller MS, Knulst AC, Meijer Y, et al. Evaluation of the child with atopic dermatitis. *Clin Exp Allergy*. 2012;42:352–362.