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Original Article

Risk factors determining the development of food allergy intolerance at the first age in infants with atopic dermatitis

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ABSTRACT

Objective: Very few studies have examined the risk factors for developing tolerance to food allergy in infants with atopic dermatitis (AD). To understand the risk factors for developing tolerance to food allergy in the first year in infants with atopic dermatitis and food allergy coexistence.

Methods: Ninety-three infants were included in this retrospective study. Food allergy was detected using food-specific IgE, skin prick, and oral food challenge tests. The severity of the disease was evaluated using Scoring Atopic Dermatitis (SCORAD). Demographic parameters were recorded from medical records.

Results: The rate of patients who tolerated food allergy in the first year was 61 (65.6%). The median age to tolerate food allergy was 12 (6-18 months). According to the SCORAD, 8 (8.6%) patients had mild, 50 (53.8%) had moderate AD, and 35 (37.6%) had severe AD. The median SCORAD value was 45.2 (35.2-54.6). There was no difference between the groups who tolerated food allergy and those who could not at the first age of life in terms of age, gender, gestational week, maternal age, and familial atopy history (p>0.05 for all). Egg allergy [p=0.035; OR:6.623 (CI:0.996-44.043)], parental atopy [p=0.024. OR:2.450 (CI:0.699-23.056], and AD severity [p=0.030. OR:1.240 (CI:1.001-22.105)] emerged as statistically significant variables at potential risk factors for food allergy intolerance in the first year.

Conclusion: Egg allergy, parental atopy, and severity of atopic dermatitis emerged as potential risk factors for intolerance to food allergy in the first year of life in infants with atopic dermatitis and food allergy coexistence.

Keywords: Atopic dermatitis, allergy, cow's milk, egg, food allergy, tolerance

INTRODUCTION

Atopic dermatitis is a chronic and inflammatory disease with itchy skin lesions, which is quite common in childhood.[1] The disease occurs due to environmental, genetic, and immunological factors that lead to impaired barrier function in the epidermis layer of the skin and immune system dysfunction.[2] Atopic dermatitis presents in the first six months of life in 45% and in the first year of life in 60% of the cases. It is classified as early-onset atopic dermatitis. Around 85% of those affected within the first five years of life.[3]

Food allergy is the leading trigger of atopic dermatitis.[3] Clinically diagnosed immunoglobulin E (IgE)-mediated food allergy has been observed in approximately one-third of infants with moderate-to-severe atopic dermatitis. It has been shown that 90% of the food allergy seen in atopic dermatitis patients is IgE-mediated.[4,5] Therefore, detecting the presence of food allergy

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plays an essential role in the prevention and treatment of atopic dermatitis.

Food allergy, like atopic dermatitis, occurs at an early age and constitutes as one of the atopic march steps.[6,7] Many studies have been conducted to support the triggering role of food in atopic dermatitis.[3] Although the incidence of food allergy in children with atopic dermatitis can be observed at different rates due to the use of different methodologies in studies, approximately 1/3 of moderate-to-severe atopic dermatitis patients have a food allergy in double-blind placebo-controlled studies demonstrated by the oral food challenge test.[7]

This study aimed to investigate the possible relationship between food allergies and the development of tolerance within the first year, and the risk factors determining tolerance in infants diagnosed with atopic dermatitis.

MATERIAL AND METHODS

The study was planned in a retrospective cross-sectional design between January 2018 – April 2020. For the study, demographic, clinical, and laboratory data were recorded from the hospital's electronic record system of the Pedaitric Allergy and Immunology outpatient clinic database. The data recorded in the system were obtained from the routine examinations of the patients at the time of diagnosis and during the follow-up. Detailed demographic characteristics were the patients' age, gender, week of birth, age of onset of symptoms, age of diagnosis, duration of symptoms, history of atopy, and presence of atopy in the family.

After evaluating the history and laboratory information in detail, the patients' existing food/foods hypersensitivity and food allergy were recorded. In the history, the nutritional status of the patients was questioned as to whether they were breast-fed or consuming milk, formula or complementary foods.

The diagnosis of food allergy was made by clinical history and/or laboratory tests, and an oral food challenge test with a suspected food trigger. For the diagnosis of food allergy, a food elimination diet was applied in which the patient's clinic was followed closely for those who could not undergo an oral food challenge test (familial preferences or a history of severe acute reaction or life-threatening reaction such as anaphylaxis with food). Food allergy was also diagnosed in patients whose symptoms improved after at least four weeks of an elimination diet.

The tolerance status of patients with food allergies was evaluated. The patient's tolerance development status was recorded after a minimum duration of 12 months to assess the tolerance situation. The patients whose records were missing were called by phone, and their tolerance status was learned by interview with the parents.

Exclusion Criteria for Infants

Patients with immunodeficiency or chronic disorders such as liver and renal disease, cancer, diabetes, and growth retardation are excluded. Patients with eczema or skin disease symptoms other than atopic dermatitis, patients using systemic or topical corticosteroids for another disease, and patients with missing data were excluded from the study.

Determination of Atopic Dermatitis Severity (SCORAD)

Atopic dermatitis disease severity scores, which were calculated routinely in the detailed physical examinations performed at the time of admission, were recorded. The atopic dermatitis severity scale (Severity Scoring of Atopic Dermatitis Index, SCORAD) was used to classify the severity of atopic dermatitis.[8]

In the evaluation, objective (A and B data) and subjective (C data) data were evaluated together, and a calculation method was used.

a. The extent of the spread of the lesions was determined according to the rule of 9s. After the body was divided into anterior and posterior facets, the body surface was divided into multiples of 9. Hands and genital area were given one point each. Thus, the lesion areas in the body were expressed as a percentage value.

b. Subjective findings 1. Erythema 2. Edema/papulation 3. Oozing 4. Excoriation 5. Lichenification 6. Dryness was evaluated by the doctor and scored between 0 and 3 (0=none;1=light; 2=medium; 3=heavy). Lesions of average weight were chosen rather than the worst skin lesions when making the evaluation.

c. The markers evaluated subjectively by the patient were pruritus and sleep disturbance. Children older than seven years of age were assessed on a scale of 0-10 according to the severity of their complaints in the last three days/nights.

All these results were calculated according to the formula A/5+7B/2+C. As a result of the total score, values below 25 points were classified as mild, values between 25 and 50 points as moderate, and values above 50 points were classified as severe atopic dermatitis.[9-11]

Parental Atopy

Parental atopy was defined as any history of allergic diseases such as asthma, hay fever, allergic eczema, or allergic conjunctivitis in one or both parents of the child.[12]

Collection of Recorded Data

Registered survey questions: gender of patients, age at admission, age of symptom onset, duration of symptoms, age at diagnosis, maternal age, family history of atopy, type of birth, presence of prematurity, presence of comorbidity, history of lung infection, history of hospitalization, presence of smoking exposure, diet (mother milk/formula/mixed/complementary), which food was suspected (cow's milk/egg/wheat/other), disease severity, duration of elimination diet, and tolerance development status.

Laboratory Findings

a. Absolute eosinophil rate and count

Absolute eosinophil counts were studied using an automated hematology analyzer (BC-6800 Hematology Analyzer, Mindray, Shenzhen, China). Absolute eosinophil rate and count results from the complete blood count were obtained from the records, and the data were included in the analysis.

b. Serum total IgE level

The total IgE level in serum samples was measured using the chemiluminescent method using an Immulite 2000 (Siemens) device in the Biochemistry Laboratory, and the results were given in the kU/L unit. Values above the normal range for age groups were considered high.

c. Evaluation of food sensitivity and allergy

Patients who had a positive response to food sIgE or at least one trigger in the skin prick test were considered sensitive to food allergens. Food-specific IgE measured using the ImmunoCAP system (PhadiaAB, Uppsala, Sweden) was considered positive if higher than 0.35 kIU/L. Food sensitivity was assessed using food-specific IgE for cow's, egg, or food panel (F5), including milk, egg, wheat, soy, peanut, and fish, and/or the skin prick test (SPT) for milk, egg, wheat, peanut, hazelnut, and soy.[12]

An induration diameter greater than or equal to 3 mm more than the diameter of the negative control was considered positive for the skin prick test. Food-specific IgE and SPT positivity were defined as food sensitivity.[12]

Food allergy was determined by oral food provocation tests. Milk, egg, formula, and other foods were used in the oral food challenge test, and the test results performed according to the recommendation of international guideline.[13]

Ethics

The study was conducted according to the principles of the Declaration of Helsinki, followed by good clinical practice, and was approved by the University Ethics Committee (2023/158).

Statistical analysis

Statistical Package for Social Science (SPSS) 21 program was used to analyze the data (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). For the descriptive statistics of the study, the median and 25-75 percentile values were used in the continuous variables since the data did not follow the normal distribution. The number and percentage were used in the categorical variables. The conformity of continuous variables to normal distribution was evaluated with descriptive statistics, steepness and skewness coefficients, histogram, and Shapiro-Wilk test. The chi-square test was used to analyze categorical data for statistical analysis. Mann Whitney U test was used to compare independent groups since the data did not fit the normal distribution. Correlations between two continuous variables were evaluated with the Spearman correlation test. Univariate logistical regression was used to identify risk factors for tolerance for food allergy. A multivariable logistic regression analysis was performed. Any Type I error level was determined as 0.05%.

RESULTS

Patient Characteristics

Ninety-three infants were included in this study. All the children with atopic dermatitis had food allergies, which were investigated using either food-specific IgE or the skin prick test and oral food provocation test. The number of patients who tolerated food allergy in the first year was 61 (65.6%). The median age of tolerating food allergy was 12 (6-18 months). The patients' demographic data are shown in Table 1.

Table 1. Demographic characteristics in children with atopic dermatitis and food allergy	
	Infants with Atopic Dermatitis and Food Allergy (n=93)
Demographic features	
Gender, n (%)	
Female	29 (31.2)
Male	64 (68.8)
Age, year; median (IQR)	4 (2-9)
Age of diagnosis, month; median (IQR)	4 (2-6)
Maternal age, years; median (IQR)	29 (26.5-32)
Gestational age, weeks; median (IQR)	39 (38-40)
Birth weight, grams; median (IQR)	3220 (2950-3500)
Prematurity, n (%)	
Yes	17 (18.3)
No	76 (81.7)
Type of birth, n (%)	
Normal spontaneous vaginal route, n (%)	33 (35.5)
Cesarean section, n (%)	60 (64.5)
Familial history of atopy; n (%)	
Yes	61 (65.6)
No	32 (34.4)
Age of symptom onset, months; median (IQR)	2 (1-4)
Symptom duration, months; median (IQR)	7 (3-14)
Distribution of lesions, n (%)	
Local, n (%)	72 (77.4)
Generalized, n (%)	21 (22.6)
SCORAD at the time of diagnosis; median (IQR)	45.2 (35.2-54.6)
Mild, n (%)	8 (8.6)
Moderate, n (%)	50 (53.8)
Severe, n (%)	35 (37.6)
First-year SCORAD; median (IQR)	30.1 (20.65-37.35)
Type of food allergy, n (%)	
IgE mediated, n (%)	30 (32.3)
Non-IgE mediated, n (%)	21 (22.6)
Mixed type, n (%)	42 (45.2)
Food allergy, n (%)	
Milk, n (%)	19 (20.5)
Egg, n (%)	35 (37.6)
Other, n (%)	4 (4.4)
Multiple, n (%)	35 (37.6)
Food allergy tolerance period, months; median (IQR)	14 (9-21)
Number of patients who tolerated food allergy in the first year, n (%)	
Yes	61 (65.6)
No	32 (34.4)
Elimination diet duration, months; median (IQR)	12 (6-18)
Laboratory features	
Absolute eosinophil	
Rate, n (%)	5.5 (3-8.48)
Count, median (IQR)	535 (310-877)
Serum total IgE level, median (IQR)	20.5 (8.25-45.75)
IQR: interquartile range, n: number, %: percentage, SCORAD: Scoring Atopic Dermatitis.	

According to the SCORAD, 8 (8.6%) patients had mild, 50 (53.8%) had moderate, and 35 (37.6%) had severe atopic dermatitis. The median SCORAD value was 45.2 (35.2-54.6).

There was no difference between the groups who tolerated food allergy and those who could not at the first age of life in terms of age, gender, gestational week, maternal age, and familial atopy history (p>0.05 for all) (Table 2).

Correlation analysis

The duration of tolerance development showed a strong positive correlation with the duration of an elimination diet in children with atopic dermatitis and food allergy coexistence (p<0.001, r=0.910). In children who developed tolerance in the first year, the duration of tolerance was positively correlated with the age of symptom onset (p=0.002, r=0.381) and the age at diagnosis (p=0.017, r=0.304). No correlation was found with any parameter in children who could not develop tolerance in the first year with any of the parameters (p>0.05).

Logistic regression analysis

Logistic regression analysis was applied to examine the effect of independent variables on food allergy intolerance in the first year of life. The predictive effect of the logistic regression analysis model was found to be 85.3% (p = 0.047, Negelkerke R2 = 0.366). Egg allergy [p=0.035; OR:6.623 (CI:0.996-44.043)], parental atopy [p=0.024. OR:2.450 (CI:0.699-23.056], and AD severity [p=0.030. OR:1.240 (CI:1.001-22.105)] emerged as statistically significant variables at potential risk factors for intolerance of food allergy in the first year. (Table 3).

Table 2. Comparison of demographic characteristics between first-year-old food tolerant and non-food-tolerant groups in children with atopic dermatitis and food allergy coexistence

	Food Allergy Those Who Tolerate (N=66)	Food Allergy Those Who Cannot Tolerate (N=27)	P value
Gender, n (%)			
Female	23 (34.8)	6 (22.2)	0.233[a]
Male	43 (65.2)	21 (77.8)	
Age, year; median (IQR)	4.5 (2-9)	4 (2-8.75)	0.392[b]
Age of diagnosis, month; median (IQR)	4 (2-6)	3 (1-6)	0.414
Maternal age, years; median (IQR)	29 (27-32.5)	29 (25-31)	0.613[b]
Gestational age, weeks; median (IQR)	39 (38-40)	38 (38-39)	0.916[b]
Birth weight, grams; median (IQR)	3250 (305-3500)	3065 (2760-3400)	0.120[b]
Type of birth, n (%)			
Normal spontaneous vaginal route	21 (31.8)	11 (40.7)	0.411[a]
Cesarean section	45 (68.2)	16 (59.3)	
Familial history of atopy; n (%)	41 (62.1)	20 (74.1)	0.271[a]
Age of symptom onset, months; median (IQR)	2 (1-4)	2 (1-4)	0.552
Symptom duration, months; median (IQR)	7 (3-14)	4.5 (2.25-14)	0.252
SCORAD at the time of diagnosis; median (IQR)	45.2 (34.85-54.05)	45.75 (34.12-55.3)	0.345
First-year SCORAD; median (IQR)	30.2 (21.25-36.1)	29.6 (18.7-44.52)	0.737

IQR: interquartile range, n: number, %: percentage, SCORAD: Scoring Atopic Dermatitis.
[a]: Categorical variables were compared using the χ2 test.
[b]: Comparison of non-normally distributed continuous variables was made using the Mann-Whitney U test.
p<0.05 is significant

Table 3. Logistic regression analysis of risk factors of intolerance of food allergy in the year of life

	B	S.E.	Wald	p	Odds ratio	95% CI	
						Lower	Upper
Parental atopy	2.798	0.775	5.164	**0.024**	2.450	0.699	23.056
SCORAD	1.039	0.031	4.178	**0.030**	1.240	1.001	22.105
Birth weight	-0.002	0.001	1.060	0.261	0.698	0.497	1.000
Gender	-1.099	0.949	1.342	0.247	0.333	0.052	6.139
Prematurity	3.156	1.613	1.829	0.145	0.475	0.395	1.927
Presence of smoking exposure	0.937	0.734	1.628	0.202	0.392	0.093	1.652
Maternal age	0.087	0.075	1.340	0.247	1.091	0.942	1.263
Presence of comorbidity	1.142	1.858	0.378	0.539	0.319	0.008	12.186
Cow's milk allergy	0.612	0.778	0.619	0.132	1.143	0.402	8.462
Egg allergy	1.891	0.967	3.826	**0.035**	6.623	0.996	44.043
History of atopy	0.156	1.178	1.594	0.247	0.043	0.004	0.429

SCORAD: Severity Scoring of Atopic Dermatitis Index, CI: Confidence Interval.
Logistic regression analysis was applied. Negelkerke R^2 of the model was 0.366. The overall percentage for the model is 85.3%. $p<0.05$ was accepted as a significance value.

DISCUSSION

In the present study, the severity of atopic dermatitis, the site of eczema involvement, the clinical course of the disease, the relationship of atopic dermatitis at the time of diagnosis with food allergy and tolerance period were evaluated in infants with atopic dermatitis. This study showed that the food allergy accompanying atopic dermatitis is mostly associated with cow's milk or egg allergy and the tolerance period is 12 months on average. The most important risk factors affecting intolerance within 12 months are the presence of egg allergy, the severity of atopic dermatitis, and the presence of parental atopy.

Atopic dermatitis presents in the first six months of life in 45%, in the first year of life in 60%, and in the first five years of life in 85% of the children.[3] In a study by Guttman-Yassky et al., the mean age of diagnosis of 21 patients with AD was found to be 1.7 years.[14] In a study conducted by Yüksel et al. with 531 children with atopic dermatitis, the mean age at diagnosis was 37.8±36.2 months.[15] The study conducted by Ulutaş et al. reported that in 298 children with atopic dermatitis, the age of symptom onset was found to be 18.1±21.5 months.[16] In this study, it was observed that the median age of symptom onset and age of diagnosis in atopic dermatitis were before the first six months of life, which aligns with the literature.

Many studies in the literature examine the relationship between atopic dermatitis and food allergy. Almost 50% of children with atopic dermatitis and 35% of adults are sensitive to environmental and food allergens, with rates ranging from 7% to 80% among different study populations. Food sensitization rates of patients range from 30% to 80%. However, clinically, the rates of food allergy may be lower, especially in the less severe phenotypes of AD. In fact, 20-30% of patients with AD have food allergies. Therefore, atopic dermatitis has been suggested as a major risk factor for food sensitization and IgE-mediated food allergy. However, symptoms suggestive of food allergy are mostly absent in patients with mild atopic dermatitis. Population-based studies have shown that patients with AD are up to six times more likely to have food sensitivities at three months of age compared to healthy controls. When hospital admissions are included, the prevalence of food sensitization is up to 66%, while proven food allergy with oral food challenges is 81%. The Danish Allergy Research Cohort (DARC) showed that up to 53% of children with atopic dermatitis aged six months to 6 years were sensitized to food allergens, with a confirmed food allergy in 15%. In Australia, in the Health Nut study, a large population-based study (n = 4453), infants with atopic dermatitis were six times more likely (95% CI 4.6-7.4) and were 11 times more likely to have a peanut allergy (95% CI 6.6-18.6).[17] In another study, moderate-to-severe children under five years of age with atopic dermatitis have shown that 37% of patients have IgE-mediated food allergies.[18]

The study of Strömberg et al. showed that in the diagnosis of food allergy in children with atopic dermatitis, these children

were shown to be sensitive to more than one food.[19] In a study by Martin et al., sensitivity to egg white was significantly higher than other foods in children with atopic dermatitis.[20] In the study conducted by Gray et al. 100 children with atopic dermatitis, food sensitivity was observed in 66% of the cases, food allergy was diagnosed in 44% by the food challenge test, and the highest rate of allergenic foods was peanut and cow's milk.[5] In our study, egg sensitivity was highest in children with AD, followed by cow's milk allergy.

Staden et al. studied the specific oral tolerance-inducing therapy (SOTI) in pediatric patients with egg or milk allergy, including the group that received an elimination diet as the control group, and examined the tolerance periods. Accordingly, the duration of tolerance development in 20 children diagnosed with food allergy whose elimination diet duration was determined as 21 months, with a minimum of 12 months and a maximum of 47 months.[21] In this study, the time to develop tolerance to food allergy may extend up to 21 months in patients with atopic dermatitis, consistent with the literature. On the other hand, there is no significant difference in demographic characteristics and severity of atopic dermatitis between patients who can and cannot develop tolerance in the first year of life.

In the present study, the most important determinants for tolerance development in the first year of life were the presence of cow's milk protein allergy, parental history of atopy, and severity of atopic dermatitis. Individuals whose family (mother, father, sibling) has a history of allergic disease (atopic dermatitis, rhinoconjunctivitis, asthma) are more likely to develop an allergic disease. In addition, associations of atopic dermatitis, rhinoconjunctivitis, and asthma, which are among atopic diseases, are frequently seen in the family histories of cases with food allergies.[22,23] In the study of Apfelbacher et al., it was observed that parental atopic diseases were significantly associated with the development of atopic dermatitis in children.[24] In another study by Lowe et al., in which the risk factors for atopic dermatitis were examined, it was shown that there was a significant relationship between the presence of allergic disease in the parents and the development of atopic dermatitis in their children.[25] It is effective on the duration of tolerance in food allergy, as well as its relationship with the presence of dermatitis and food allergy. On the other hand, it has been shown that 70% of infants with atopic dermatitis recover from the disease in late childhood. Still, in those with early or severe onset atopic dermatitis, in the presence of a family history of atopic dermatitis and sensitization to allergens at an early age, the disease recovers at a later age.[26] While 43.2% of patients with early-onset atopic dermatitis had complete recovery after two years of age, 38% of patients with early-onset atopic dermatitis continued to have intermittent atopic dermatitis flare-ups until seven years of age. Disease severity and early sensitization (especially food sensitivity) were found to be among the poor prognostic factors in severe atopic dermatitis.[27] There is a higher rate of allergic sensitization in patients with early-onset and severe AD, and it has been reported that patients with AD are associated with sIgE positivity. Accordingly, it is thought that the severity of the disease affects the natural course of allergic sensitization and the atopic march in AD.[15] Similarly, having severe atopic dermatitis is a risk factor for a longer recovery from food allergy. The prevalence of food allergy is higher in children than in adults; in prospective studies of adverse food reactions in young children, about 80% outgrow their problem after the third year of life. One-third of food-allergic patients lose their sensitivity after two years of avoiding diet. The study of Pascual et al. showed that egg white protein is the most common allergen, followed by cow's milk and peanuts. These three food items represent half of the sensitizations in children under two years of age. Patients with milk allergies are more prone to losing their sensitization one or two years earlier than those allergic to eggs.[28] In our study, consistent with the literature, egg allergy was found to be a risk factor for food intolerance.

The strengths of the study are that it was conducted in a tertiary health centre where allergic diseases in children were evaluated in detail, the diagnosis of food allergy was made with a food challenge test, and food allergy sensitivity in infants was assessed with standardized food-specific IgE or skin prick tests. The fact that patients with atopic dermatitis are evaluated and recorded with their SCORAD in every visit in our clinic and the absence of missing data in patient records does not cause data loss in the analyses strengthened our results.

The limitations of the study are that the study design is retrospective, there is no healthy control group, and cases with food tolerance after the 12th month in the patient follow-ups cannot be evaluated. The fact that the study was conducted in a tertiary reference centre may cause more severe cases to be included in the evaluation. Therefore, it is not possible to generalize the results obtained to the general population.

CONCLUSION

In this study, egg and milk were found to be the most common allergens in concomitant food allergy in infants with atopic dermatitis. Tolerance to food allergy develops in more than half of infants by 12 months. Risk factors affecting the development of tolerance to food allergy in the first year of life were found to be the presence of hen's egg allergy, the severity of atopic dermatitis, and the presence of parenteral atopy. The results of this study provide us with important data in the close follow-

up of the development of tolerance in the clinical follow-up of the patients. The results of this study need to be confirmed with prospectively designed studies. We think that our results will be a light for future studies and will help determine individualized treatment approaches by more clearly revealing the risk factors affecting the development of tolerance.

Ethical approval

Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Ethics Committee approved the protocol of the study (Approval number: 2023/158). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: BVM, PU; Concept: BVM, PU; Design: BVM, PU; Data Collection or Processing: BVM, PU; Analysis or Interpretation: BVM, PU; Literature Search: BVM, PU; Writing: BVM, PU. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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