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Evaluation of Probiotic Use in Children With and Without Allergic Diseases

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Abstract

Aim: Various studies have reported that probiotics play a role in immune modulation and in preventing the development of allergic diseases by affecting the intestinal flora. However, there is no clear consensus on this subject yet. This study aimed to evaluate the usage of probiotics in children with and without allergic diseases.

Method: Probiotic usage of children (<18 years old) with and without allergic disease, who applied to the tertiary care pediatric immunology and allergic diseases clinic between 26,December 2023 and 26,January 2024, was evaluated cross-sectionally. Demographic characteristics of the patients, presence of allergic diseases, exposure to pets and cigarettes, and probiotic use (at any time and during the neonatal period) were recorded.

Results: A total of 381 patients (57.7% male) with a median age of 7,5 years(IQR:5-10,7) were included in the study. Of the children 269 (70.6%) with allergic disease and 112 (29.4%) without allergic disease. A total of 190 (49.8%) patients had used probiotics at any time; of these, 77 (40.5%) used for colic in the neonatal period. When patients with and without allergic diseases were compared, the median age, time of birth, type of birth, frequency of family atopic diseases, smoking exposure, pet exposure and frequency of probiotic usage at any time were similar (p respectively: 0.283, 0.507, 0.909,0.122, 0.308,0.486,0.552). Male gender (62%) was more common in those with allergic diseases,(p:0.008). Probiotic usage during the neonatal period was higher in patients without allergic diseases than in those with allergic diseases (32.1% vs 15.2%; p: <0.001).

Conclusion: Our study found that half of the children had used probiotics at some point in their lives. Notably, probiotic use during the neonatal period was higher among children without allergic diseases compared to those with allergic diseases, supporting the hypothesis that early-life probiotic supplementation may have a protective effect against atopic diseases. However, differences between the type, dose, and duration of probiotics administered in the studies cause difficulties in comparing and generalizing the results. So, standard, molecular level and with longer follow-up periods studies are needed.

Keywords: allergic diseases, allergic rhinitis,asthma, atopic dermatitis, food allergy, probiotics, prophylaxis

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Alerjik Hastalığı Olan ve Olmayan Çocuk Hastalarda Probiyotik Kullanımlarının Değerlendirilmesi

Öz

Amaç: Probiyotik kullanımının intestinal florayı etkileyerek immün modulasyonda ve alerjik hastalıkların gelişmesini engellemede rolü olduğu bildirilmektedir. Ancak bu konudaki literatür hala net bir görüş birliğine ulaşmamıştır. Bu çalışmada alerjik hastalığı olan ve olmayan çocuk hastaların probiyotik kullanımlarının değerlendirilmesi amaçlanmıştır.

Yöntemler: 26 Aralık 2023 ve 26 Ocak 2024 tarihleri arasında üçüncü basamak Çocuk İmmünolojisi ve Alerjik Hastalıklar Kliniği'ne başvuran alerjik hastalık saptanan ve saptanmayan çocuk (<18 yaş) hastaların probiyotik kullanımları kesitsel olarak değerlendirilmiştir. Hastaların demografik özellikleri, alerjik hastalık durumları, evcil hayvan ve sigara maruziyetleri ile probiyotik kullanımları (herhangi bir zamanda ve yenidoğan döneminde) standart veri formlarına kaydedilmiştir.

Bulgular: Alerjik hastalığı olan 269 (%70,6) ve alerjik hastalık olmayan 112 (%29,4) çocuk hasta olmak üzere 381 hasta çalışmaya dahil edildi. Hastaların yaş ortancası 7,5 yaş (ÇAA= 5-10.7) olup % 57.7 si erkekti. Toplamda 190 (%49,8) hasta herhangi bir zamanda probiyotik kullanmıştı; bunların 77'si (%40,5) yenidoğan döneminde kolik için probiyotik kullanmışlardı. Alerjik hastalığı olan ve olmayan hastalar karşılaştırıldığında yaş ortancalarının, doğum zamanı, doğum şekilleri, ailede atopi sıklıkları, sigara maruziyetleri, evcil hayvan maruziyetleri ve herhangi bir zamanda probiyotik kullanım sıklıkları benzerdi (p sırası ile: 0.283, 0.507, 0.909,0.122, 0.308,0.486,0.552). Alerjik hastalığı olanlarda erkek cinsiyet (%62), alerjik hastalığı olmayanlarda ise kız cinsiyet (%52,7) daha sıktı (p:0.008). Alerjik hastalığı olmayanlarda yenidoğan döneminde probiyotik kullanımı alerjik hastalığı olanlara göre daha yüksekti (%32,1 vs %15,2; p: <0.001).

Sonuç: Çocuk hastaların yarısı herhangi bir yaşta probiyotik kullanmıştı. Alerjik hastalığı olmayan hastaların yenidoğan döneminde probiyotik kullanımlarının alerjik hastalığı olan hastalara göre daha yüksek olduğu görüldü. Elde edilen bulgular, yaşamın erken evrelerindeki probiyotik desteklerinin immün modulasyonu etkileyerek atopik hastalıklara karşı koruyucu bir rol oynayabileceği hipotezini desteklemektedir. Fakat çalışmalardaki uygulanan probiyotik türü, dozu ve süresi arasındaki farklılıklar; sonuçların karşılaştırılmasını ve genellenmesini zorlaştırmaktadır. Bunun için standart, moleküler düzeyde ve daha uzun takip süreli yeni çalışmalara ihtiyaç vardır.

Anahtar kelimeler: alerjik hastalıklar, alerjik rinit, astım, atopik dermatid, besin alerjisi, probiyotik, profilaksi.

INTRODUCTION

The prevalence of allergic diseases has been reported to increase globally over the years, with a more pronounced increase in developed countries compared to developing countries[1]. Factors that may cause this rise are still being studied and the hygiene hypothesis is reported as one of the important attributable factors for this in several studies[2,3]. It has been shown that increasing hygiene conditions affect the microbiota, leading to a decrease in the TH1 response and an increase in the Th2 response, thus increasing allergic diseases[3].

Gut microbiota affects the immune system by making some immune modulation; so altered microbiota, especially during early life periods attributed to one of the causes of developing allergic diseases[3,4]. Therefore, some preventive strategies have been tried to be developed in this regard. Probiotic supplementation was studied in some cohorts and showed that children who were taking probiotics became less allergic later years[5,6]. But dosage, type, duration and necessities of probiotics are still unknown. In contrast to other studies, several studies did not show a relationship between probiotics and allergic diseases, especially in the cases of asthma, atopic dermatitis, and food allergies[7,8]. Therefore, uncertainty on this issue continues. But some preventive strategies for protecting microbiata is recommended in several studies and guidelines such as preventing unnecessary ceserian birth, unnecessary antibiotic usage and unhealthy nutrition[9-11].

In this study, we aimed to evaluate the usage of probiotics in children with and without allergic

diseases to investigate whether there is a difference.

METHODS

Study population

Children were categorized into two groups based on the owning of allergic diseases. The data was collected retrospectively from medical records, covering the period between December 26, 2023, and January 26, 2024.

Study procedure

Patient data were recorded using a standardized form that included demographic and clinical characteristics. Detailed information regarding the presence of allergic diseases was collected retrospectively from medical records. In our clinic, a standard anamnesis form is uniformly employed for all patients ensuring consistent inquiry into the presence of any diseases, medications and/or supplements (such as vitamins, probiotics, and minerals). If any are present, detailed information is obtained. Additionally, the form captures risk factors for allergic diseases (such as exposure to cigarette smoke, pets, molds, and antibiotics during the neonatal period) and preventive strategies (such as vaccines). Additionally, baseline eosinophil count and percentage, along with total IgE levels at presentation, were documented.

Diagnosis of allergic diseases

Diagnoses of food allergy, allergic rhinitis (AR), atopic dermatitis (AD), and asthma were established by relevant guidelines by allergy and immunology physicians within the research team[12-15].

Control group

The control group was selected retrospectively by reviewing patient medical records. These patients were randomized and evaluated by study physicians to ensure they did not have any allergic diseases.

Definition of probiotics

Probiotics is called as live bacterial supplemental preperats when administered adequately cause a significant health benefit on the patients[16].

Statistical analysis

Data analysis was conducted using SPSS version 22.0 (IBM Corp, Armonk, NY). Continuous variables were expressed as the median and interquartile range (IQR, 25th-75th percentiles). Chi-squared ($\chi 2$) and Fisher's exact test were used for comparisons of qualitative variables, while Mann-Whitney U and Wilcoxon rank sum test were used for comparisons of quantitative variables. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 381 patients, of whom 57.7% were male, were included in the study. The median age of them was 7,5 years (IQR:5-10,7). The characteristics of the children are presented in Table I. Patients were stratified into two groups based on the presence of allergic disease: of the children 269 (70.6%) had allergic disease and 112 (29.4%) didn't have allergic disease. The distribution of the allergic diseases in children is outlined in Figure 1. And distribution of the allergen sensitization of children with allergic diseases is outlined in Figure 2.

Table I: Demographic characteristics of patients (n: 381)

Age , (year), median(IQR)	7.5 (5-10.7)
Gender,(male), n (%)	220 (57.7)
Mode of delivery,(cesarean), n(%)	162 (42.5)
Premature birth, n(%)	31 (8.1)
Birth weight, median(IQR)	3100 (2850-3500)
Hospitalisation during neonatal period, n(%)	35 (9.2)
Family atopy, n (%)	115 (30.2)

IQR: inter quartile range

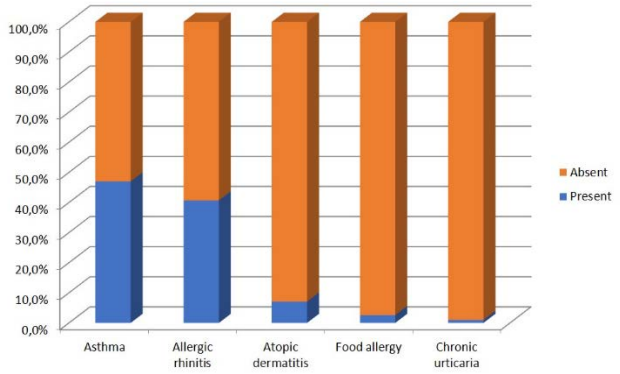

Figure 1: Distribution of the allergic diseases of children

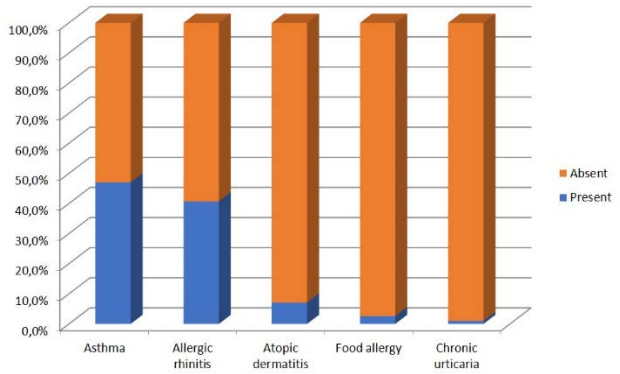

Figure 2: Distribution of allergen sensitization of patients

Probiotics

Among the patients, 190 (49.8%) children had used probiotics at any time. Of these, 77 (40.5%) used in the neonatal period.

Comparison of Patients with and without allergic diseases

There weren't any differences in potential confounders, such as type of delivery, birth order, maternal atopy, breastfeeding, antibiotics and probiotic supplementation, between the infants with and without allergic diseases. The similarities and differences between the children with and without allergic disease are delineated in Table II. Male gender (62%) was more common in those with allergic diseases,(p:0.008). Probiotic usage during the neonatal period was higher in patients without allergic diseases than in those with allergic diseases (32.1% vs 15.2%; p: <0.001).

Table II: Comparison of patients with and without allergic diseases

	With allergic diseases n:269	withoutallergic diseases n:112	p
Age (years), median (IQR)	8 (5-11)	6,5(4.6-10.3)	0.283
Gender (male), n (%)	167 (62)	53 (47.3)	0.008
Mode of delivery (C/S), n (%)	115 (42.7)	47 (41.9)	0.909
Preterm birth, n (%)	24 (8.9)	7 (6.2)	0.57
Family atopy, n (%)	88 (32.7)	27 (24.1)	0.122
Probiotic useage at any time, n (%)	131 (48.6)	59 (52.6)	0.552
Probiotic useage at neonates, n (%)	41 (15.2)	36 (32.1)	0.000
Cigarette usage of family, n (%)	103 (38)	36 (32.1)	0.308
Pet keeping, n (%)	48 (17.8)	16 (14.2)	0.486

C/S: Ceserean sectio,IQR: inter quartile range

Comparison of patients with and without the use of probiotics at any age and during the neonatal period

Similarities and differences between the children with and without probiotic usage are delineated in Table III.

Table III: Comparison of patients with and without probiotic usage

At any time				At neonatal periods		
	With Probiotic usage n:191	Withoutprobiotic usage n:190	p	With Probiotic usage (n:77)	Withoutprobiotic usage (n:303)	p
Gender (male), n (%)	112	108	0.751	45 (58.4)	175 (57.7)	1
Family atopy, n (%)	64	51	0.170	23 (29.8)	92 (30.3)	1
Allergic disease, n (%)	131	138	0.552	**41 (53.2)**	**228 (75.2)**	**0.000**
Asthma, n (%)	89	90	0.957	28 (36.3)	151 (49.8)	0.050
Allergic rhinitis, n (%)	79	76	0.722	31 (40.3)	124 (40.9)	1
Food allergy, n (%)	8	2	0.107	**6 (7.8)**	**4 (1.3)**	**0.001**
Atopic Dermatitis, n(%)	13	14	0.853	5 (6.4)	22 (7.2)	1

The frequency of allergic diseases, especially food allergy, is less common in children who used probiotics during the neonatal period (p respectively; <0.001 and <0.001).

According to regression analysis; while probiotic usage during neonates (OR:0.36 [0.21-0.62];p:0.005) was detected as a protective factor; male gender (OR:1.92 [1.21-3.03]; p:0.00) was detected as a risk factor for having any allergic diseases (Table 4).

Table IV: Factors that were affectedby having the allergic disease

	UNİVARİANT			MULTİVARİANT		
	OR	CI %95	p	OR	CI %95	p
Male gender	1.82	1.16-2.84	0.008	1.92	1.21-3.03	0.005
Cesarean birth	1.05	0.67-1.64	0.820			
Probiotic usage at any time	0.85	0.54-1.32	0.479			
Probiotic usage during neonates	0.38	0.22-0.63	0.00	0.36	0.21-0.62	0.00
Family atopy	1.50	0.92-2.52	0.097	1.60	0.95-2.68	0.067
Cigarette exposures	1.31	0.82-2.08	0.257			
Pet keeping	1.30	0.70-2.40	0.39			

DISCUSSION

This study sheds light on the comparison of the usage of probiotics in children with and without allergic diseases. We found that the frequency of probiotic usage at any age was similar in children with and without allergic diseases, but probiotic usage during neonatal periods was approximately two times more frequently seen in children without allergic diseases than children with allergic diseases.

The prevalence of allergic diseases has been reported to rise globally over the years and more prevalently increased in developed countries than in developing countries[1,5]. Some factors which stimulate the immune system are effect the development of allergic diseases[5,17]. Gut microbiata is one of these factors to stimulate the immune systems and effects the its maturations[5,18,19]. Perinatal dysbiosis causes reduced Th1 cytokine response and delays in the immune system maturations of children[19]. Probiotic supplements such as Lactobacilli and Bifidobacteria can increase the Th1 levels, so providing the balance with Th2 and so maturation of immunity[19].

Gastrointestinal tracts of neonates are considered to be sterile at birth and become colonized by environmental microbiota, especialy from the mother, during delivery[4,20]. There were some factors considered to affect the colonisations of the gut establishing after birth to during infancy such as type of delivery (cesarean versus vaginal), infections, antibiotic treatment, breastfeeding, type of nutrition, and probiotic usage[5,19,21,22]. Intestinal microbiota which modulates the immune systems; reaches the mature levels near two years old; so some interventions may change the composition of intestinal microbiata especially during perinatal periods and until 2 years old[19,22]. Several studies showed that supplementation of the live bacterial preperats may have health protective effects via affecting gastrointestinal systems[2,23].

These live bacterial supplemental preperats which is called probiotics was defined by Food and Agriculture Organization of the United Nations-World Health Organization (FAO-WHO) that live microorganisms when administered in adequate amounts confer a significant health benefit on the host[16]. Generally, they are documented and considered as safe preperats20; so are frequently used as a

supplement therapy such as for diarrhea, colics and during anti-biotherapy usage[16,24,25]. In our study half of the children used probiotics at any age. Of these, 40.5% were used in the neonatal period.

Primary and secondary prophylactic interventions are important for preventing allergic diseases[22]. Several studies has been hypothesed that manipulation of the intestinal microbiome in infants during early life may help to prevent to develop some allergic diseases[5,18]; since several studies were reported that diversity of the gut microbiata were difer between allergic and non allergic children[26,27]. Feleszko W and et al reported that probiotic applications to the mice during the neonatal period decreased to the atopic sensitization and atopic airway disease in a murine model of asthma[2]. In a population based cohort study, including 40 614 mother–child pairs, dedicated that associations between consumption of probiotic milk products in pregnancy and infancy with questionnaire-reported allergic diseases including atopic dermatitis, asthma and rhinoconjuctivitis. And they detected that consumption of milk with probiotics during pregnancy was associated with a lower incidence of eczema and rhinoconjunctivitis, but not asthma, at 3 years of age[18]. This study supported that the probiotic usages in prenatal and early life periods may provide protective effects from allergy in the population[21]. Kukkonen K and et al in their probiotic intervention study (they give probiotic preparation to the mother for 2 to 4 weeks before birth and to children for 6 months) reported that probiotic treatment does not influence to the development of all allergic diseases until 2 years of age but significantly influenced to development of eczema and especially atopic eczema[28]. Morrisset and et al reported that probiotics containing Formula feeding decreased the development of food allergies, especially cow milk allergy[29]. Similarly, in this study, we didn't detect all allergic diseases were differ in children with and without probiotic usage at neonate; too. We detected that food allergy and having any atopic diseases were high in patients without probiotic usage at neonate than patients with. Asthma, allergic rhinitis and eczema didn't significantly differ between groups. So results are changeable from study to study; so stil there is not enough evidence about the welfare of using probiotics in protection or treating of allergic disease[8,21]. New, case-control, longitudinal studies are necessary.

On the other hand; other than probiotics some other factors may affect to microbiota and so the development of allergic diseases; such as Kallio Sampo and et al reported that gastrointestinal colonisations at 3 months were mainly associated with the type of birth, usage of antibiotics (0–6 months), and breastfeeding exclusively and usage of probiotics, with probiotic treatment causing for the largest microbiota variation[5]. So while evaluating the efects of the probiotic interventions; these factors may take to attention as a confounding factors. Ceserean section may affect the diversity of microbiota and may reduced TH1 responses in early life[4,30]; so it may be a confounding factor for our study. But in our study there weren't any significant differences in birth with cesarean section between healthy and allergic groups. Also, age, birth time, and family atopies are very similar between children with and without probiotic usage.

There were some limitations in our study. First of all because of the retrospective manner of our study there may be remembering bias of parents. Duration and dosage may affect the results but we didn't reach the knowledge of the duration and dosage of probiotic usages so this was the second limitations of our study. And our study is based on only parental reports so it may be subjective. However, our samples were chosen definitely according to allergy physician

evaluation as allergic and non-allergic. And same questions were asked of parents of children with and without allergic diseases by allergy physicians. So single single-centered study is the strongest way of our study. Also our study showed that probiotic usages of patients without allergic diseases were more frequent than patients with allergic diseases where as there weren't any diffences of probiotic usages at any time between groups. So our results support the previous studies.

In conclusion; Half of the children had used probiotics at any time. It was observed that the usage of probiotics in the neonatal period of children without allergic diseases was higher than in children with allergic diseases. Our result comfort to the hypothesis that probiotic supplementation at early life, may cause protective effect against to atopic diseases by modulating the immune system. However, differences between the type, dose and duration of probiotics administered in the studies cause difficulties to compare and generalize the results. Future studies should focus on standardized molecular approaches and include longer follow-up periods to validate these findings.

Ethics Committee Approval: Approval was obtained from the local ethics committee (Decision no: E-24/43).

Conflict of Interest: The authors declared no conflicts of interest.

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