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ARAŞTIRMA RESEARCH ARTICLE

Does mode of delivery affect asthma developing in children who had neonatal sepsis?

Doğum şeklinin yenidoğan sepsisi geçirmiş çocuklarda astım gelişimine etkisi var mı?

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ABSTRACT

Objective: The aim of this study is therefore to evaluate whether mode of delivery (normal versus elective cesarean section) has an influence on the development of asthma in children who had neonatal sepsis. It is known that neonatal sepsis and mode of delivery have some effect on children developing asthma, but no study has evaluated both of these factors in the same group.

Materials and Methods: Patients born either vaginally (n= 15) or via elective C-section (n= 20) with proven sepsis and their healthy siblings born either vaginally (n= 20) or via elective C-section (n= 20) were included in the study. All children were evaluated with ISAAC questionnaires, physical examination, eosinophil counts, serum IgE levels, and aeroallergen sensitivity via the Phadiatop test.

ÖZ

Giriş: Bu çalışmanın amacı; doğum şeklinin yenidoğan sepsisi geçirmiş olan çocuklarda astım gelişimine etkisi olup olmadığını araştırmaktır. Yenidoğan sepsisi ve doğum şeklinin çocuklarda astım gelişimi üzerine etkisi olduğu bilinmektedir, ancak her ikisinin aynı grupta değerlendirildiği bir çalışma yoktur.

Gereç ve Yöntem: Çalışmaya kanıtlanmış sepsis geçirmiş yenidoğanlar [vajinal yolla (n= 15), elektif sezaryenle (n= 20)] ve onların sağlıklı kardeşleri [vajinal yolla (n= 20), elektif sezaryenle (n= 20)] alındı. Bütün çocuklar ISAAC anketi, fizik muayene, eozinofil sayısı, serum IgE seviyesi ve phadiotop testiyle değerlendirildi.

Bulgular: Belirgin hastalık tanımlama ve alınma kriterleri kullanıldığı için çok az allerjik çocuk belir-

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Results: Only a few allergic infants were observed when they were evaluated with strict inclusion and disease definition criteria. In addition, adjusted risk ratios indicated that both mode of delivery and sepsis had no risk in the development of asthma and allergic diseases.

Conclusion: When evaluated with strict inclusion and disease definition criteria, we observed that neither sepsis nor mode of delivery affected the development of asthma in these children.

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lendi. Risk oranları, astım ve allerjik hastalık gelişimine doğum şekli ve sepsis geçirmiş olmanın etkisi olmadığını gösterdi.

Sonuç: Belirgin hastalık tanımı ve alınma kriterleri ile değerlendirildiğinde astım gelişimine doğum şekli ve yenidoğan döneminde sepsis geçirmenin etkisi olmadığı gözlendi.

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Anahtar kelimeler: Astım, doğum şekli, sepsis, hastalık tanımı

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INTRODUCTION

The reasons for the increasing incidence of childhood asthma and allergic diseases remain unclear. Birth cohort studies are useful for identifying risk factors[1]. The hygiene hypothesis, as a risk factor, comes close to explaining the connection between decreasing infections and increasing allergic and autoimmune diseases related to Th1/Th2/Treg and the newer T-cell subgroups[2,3]. However, the precise mechanisms still remain unclear. Thereby, asthma is believed to be a complex, heterogeneous disorder with several molecular mechanisms[3]. Impact of different asthma definitions is another possibility to the results of researches. As mentioned in a recent meta-analysis, 122 papers yielded 60 different definitions of asthma[4]. At present, it doesn't seem reached a consensus on how to define the diagnosis of allergic diseases with questionnaires[5].

Some studies have reported a decreased prevalence of asthma in children who had neonatal sepsis[6,7]. Other findings have indicated that cesarean section (C-section) delivery might have an effect on the development of allergic diseases related to gut flora modulation and other factors[8-10].

Given these previous findings, we attempt to evaluate the hypothesis that atopic diseases and asthma should be seen less frequently in children who had neonatal sepsis and were born vaginally. Additionally, we used strict inclusion and disease definition criteria in the study groups.

MATERIALS and METHODS

Assessment of Participants

The neonatology clinic at the Faculty of Medicine at Ondokuz Mayis University comprises two divisions, level 2 and level 3, and has 30 incubators and 14 ventilators. The number of patients is about 1,000-1,200 per year; therefore, it is the only reference center in the Black Sea Region of Turkey. According to the level 2 registrations, among the 5100 patients in the period between January 2003 and January 2008, there were 105 term and appropriate for gestational age (AGA) newborns that had been diagnosed with sepsis determined by clinical and laboratory findings (by AY). After Institutional Review Board of Ondokuz Mayis University approved the study, registrations of 98 of them were reached. The accounted sample size was 20 infantsborn vaginally and 20 infants born by elective C-section (no labor effect) with 85% power. Infants that showed clinical evidence of sepsis such as tachypnea, bradypnea, dyspnea, apnea, cyanosis, and lethargy were included in the study if there was a positive blood culture (proven sepsis) or at least one laboratory finding (WBC > 15.000/mm^3, positive C-reactive

protein (CRP) (> 3 mg/dL), I/T > 0.1; presumed sepsis) andif their parents agreed to participate with signed informed consent form[7,11]. Among these 98 newborns, 15 were born vaginally and 20 were born by elective C-section. As a control group, siblings nearest in age were included because of the minimal environmental and genetic effectand if they had no sepsis during the neonatal period. Of the children in the control group, 20 were born vaginally and 20 were born by elective C-section.

Exclusion criteria were as follows: maternal fever, atopy, connective tissue disease, autoimmune disease, immune deficiency, premature membrane rupture (> 18 hour), chorioamnionitis, meconium-stained amniotic fluid, placenta previa, abruptio placenta, antenatal steroid or drug use by the mother, breech presentation, plural gestation, congenital abnormality, Apgar score < 7, prematurity (< 37 weeks), small for gestational age for newborns. For neonatal immune response standardization, premature membrane rupture, chorioamnionitis, and nonelective C-section delivery were also excluded.

ISAAC Questionnaire

After giving their informed consent, mothers filled out three modules of the standard ISAAC questionnaire translated into Turkish [5,7,12,13].

Physical Examination

All children were examined by the same researcher (EA) for Dennie's lines and conjunctival hyperemia for allergic conjunctivitis; serous nasal discharge, nasal grooving, and mucosal paleness for allergic rhinitis; skin dryness, and itching tracks for atopic dermatitis; chest deformity and pathologic breath sounds (wheezing or rhonchi) for asthma[14].

Laboratory Evaluations

Blood samples were collected from all children, 2 cc in the EDTA tube for CBC and 3 cc in the normal tube for the respiratory allergen screening test (Phadiatop). Total eosinophil count was determined with CBC by a Coulter counter in the Ondokuz Mayis University Hospital Central Laboratory.

Blood samples in the normal tubes were centrifuged at 3000 rpm for 5 minutes and then the separated serum was divided into two plastic serum tubes. One of the tubes was used for determining total serum IgE level via a nephelometric method in the Ondokuz Mayis University Hospital Central Laboratory (cut off level 17 kU/L).The other sample was stored at -80°C. At the end of the study, these samples were used to conduct the respiratory screening test (Phadiatop, specific IgE) in Duzen Laboratory (Ankara-Turkey). If a participant had a serum-specific IgE level higher than 0.35 kU/L, he or she was accepted as atopic[15-17].

Disease Definitions

If a participant responded positively to the second and sixth questions of the asthma module of the ISAAC questionnaire and the total score was higher than 6, and if this participant had at least one respiratory finding on the physical evaluation and total serum IgE was higher for his or her age or the participant had a positive Phadiatop test, he or she was diagnosed with doctor-diagnosed asthma[5,12,13]. If a participant responded positively to the first and second questions of the allergic rhinitis module of the ISAAC questionnaire and the total score was higher than 8, and if this participant had a positive Phadiatop test, he or she was diagnosed with doctor-diagnosed allergic rhinitis[13]. If a participant responded positively to the first and third questions of the atopic eczema module of ISAAC questionnaire and the total score was higher than 7, andif this participant had a higher total serum IgE for his or her age, he or she was diagnosed with doctor-diagnosed atopic eczema[16,17].

Statistical Analysis

Statistical analyses were performed by the Department of Biostatistics at Ondokuz Mayis University. Because of groups were small, Fisher's exact test was used for comparisons between groups. Values of $p< 0.05$ were considered statis-

tically significant. Data for these analyses are presented as relative risks with 95% confidence intervals (CI).

RESULTS

To address the effects of mode of delivery on the development of allergic diseases, especially asthma, in children who had sepsis during the newborn period, we had planned to analyze 20 children for both modes of delivery (vaginal and elective C-section). Of the 105 children in our registry for this period, only 15 children met the inclusion criteria in the vaginal delivery group. Excluding premature membrane rupture, chorioamnionitis, non-elective C-section, and prematurity as important risk factors for neonatal sepsis may have resulted in the lower number of participants.

Children who had neonatal sepsis and were born by vaginal delivery were included in Group 1, children who had neonatal sepsis and were born by elective C-section in Group 2, siblings who did not have neonatal sepsis and were born by vaginal delivery in Group 3, and siblings who did not have neonatal sepsis and were born by elective C-section in Group 4. As shown in Table 1, there were no different demographic- and sepsis-related findings among the groups. However, gender distribution was completely incidental and the children in the sepsis group were naturally younger.

There were only a few allergic infants when they were evaluated with these strict inclusion and disease definition criteria. In addition, comparisons were not different among the groups (Table 2, Figure 1). Similarly, when groups were analyzed for the risk factor of sepsis [RR = 2.286 (0.465; 11.25), 95% CI] and for the risk factor of mode of delivery [RR = 4.375 (0.657; 29.50), 95% CI], adjusted risk ratios indicated that neither situation was a risk for the development of doctor-diagnosed asthma. Analyses of the groups for the risk factor of sepsis [RR = 0.438 (0.044; 4.371), 95% CI] and for the risk factor of mode of delivery [RR = 1.73 (0.487; 5.131), 95% CI] showed that neither situation was a risk in the development of doctor-diagnosed allergic rhinitis and doctor-diagnosed atopic eczema [RR = 1.714 (0.307; 9.567), 95% CI] and [RR = 3.5 (0.475; 25.810), 95% CI]. In fact, a comparison of groups according to the atopy-related tests (i.e., high eosinophilia, total serum IgE, and Phadiatop test) showed similar results.

Table 1. Comparison of some demographic and neonatal sepsis-related data for the groups

	Actual age (year) X ± SD Median	Genus (F/M)	Birth weight X ± SD Median	Breastfed (/month) X ± SD Median	Passive smoking n (%)	Sepsis (E/L)	WBC ↑	CRP ↑	I/T ↑	Positive culture
Group 1 (n= 15)	3.5 ± 1.8 4.2	4/11	3325 ± 603 3310	8.4 ± 7.76 7	6 (40)	7/8	7	9	3	7
Group 2 (n= 20)	3.5 ± 1.8 4	8/12	3058 ± 441 3075	5.9 ± 5.3 4.5	8 (40)	10/10	10	11	6	7
Group 3 (n= 20)	8.5 ± 1.6 9	11/9	3277 ± 590 3275	7.2 ± 5.1 6	10 (50)	-	-	-	-	-
Group 4 (n= 20)	7.3 ± 2.3 7.7	13/7	3334 ± 458 3300	7.9 ± 7.1 6	11 (55)	-	-	-	-	-
p				0.240	0.13		0.497	0.780	0.681	0.511

I/T: Immature/total, E/L: Early/late

[In this study, patients born either vaginally (n= 15) or via elective C-section (n= 20) with proven sepsis and their healthy siblings born either vaginally (n= 20) or via elective C-section (n= 20) were included to evaluate mode of delivery effect on asthma developing. Only a few allergic infants were observed]

Table 2. Comparison of the groups according to the diagnoses for allergic diseases

	Asthma n (%)	Allergic rhinitis n (%)	Atopic eczema n (%)	Asthma + Allergic rhinitis n (%)	Asthma + Atopic eczema n (%)
Group 1	1 (6)	0 (0)	1 (6)	0 (0)	1 (6)
Group 2	3 (15)	2 (10)	2 (10)	2 (10)	0 (0)
Group 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Group 4	2 (10)	1 (5)	2 (10)	1(5)	0 (0)
p	0.088	0.336	0.134	0.89	0.99

[In this study, patients born either vaginally (n= 15) or via elective C-section (n= 20) with proven sepsis and their healthy siblings born either vaginally (n= 20) or via elective C-section (n= 20) were included to evaluate mode of delivery effect on asthma developing. Only a few allergic infants were observed]

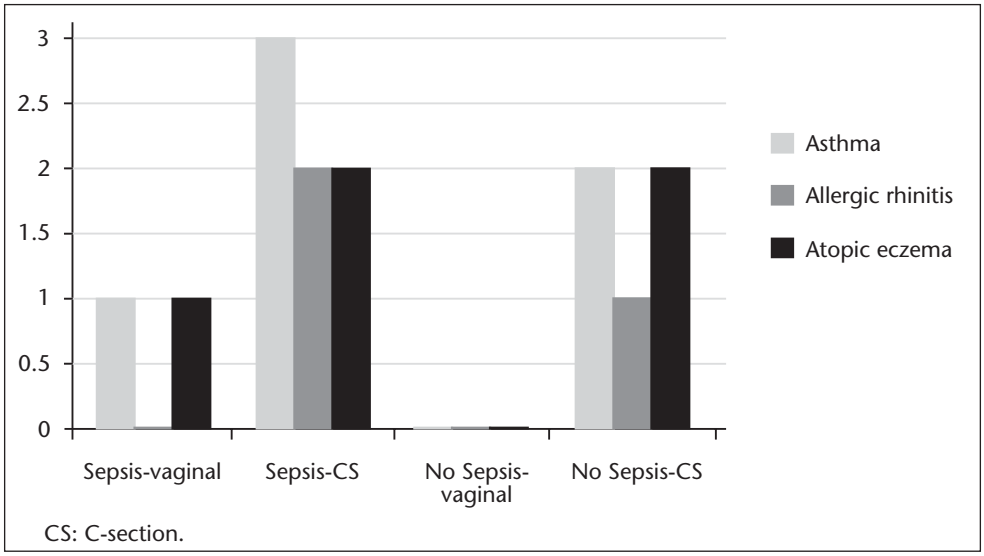

Figure 1. All atopic diseases were seen much more frequently in Group 2, namely, those children who did have neonatal sepsis and were born by elective C-section but, probably due to the small sizes of the study groups, this finding was not statistically significant.

DISCUSSION

We hypothesized that atopic diseases and asthma would be seen less frequently in children who had neonatal sepsis if they had been born vaginally. Although we planned to evaluate 20 children for each group but our inclusion criteria were so rigid that only 15 children could be included in the vaginal delivery group. As the demographic- and sepsis-related data show (Table 1), almost all possible perinatologic factors that could affect the study were excluded. All questionnaires were filled out by the mothers of the participants upon request. To eliminate the subjectivity of the questionnaires, a scoring system combining responses to the questionnaire, physical examination results, and laboratory test results was used for final diagnoses[5,13]. However, we need to sign that gender distribution was completely incidental and the children in the sepsis group were naturally younger. The age and number of siblings can also play role in allergy development. The siblings (non-septic) had probably more passive smoking that could be the risk factor of respiratory allergy.

Asthma was more seen in children who had neonatal sepsis and were born by elective C-section (one in Group 1 and three in Group 2)

Table 3. Comparison of groups according to the atopy related tests

	Eosinophilia* (/mm^3) n (%)	High total serum IgE# (kU/L) n (%)	Positive Phadiatop (kU/L) n (%)
Group 1	3 (20)	8 (53)	4 (27)
Group 2	3 (15)	8 (40)	4 (20)
Group 3	3 (15)	6 (30)	3 (15)
Group 4	4 (20)	9 (45)	3 (15)
p	0.445	0.479	0.882

* Eosinophilia > 400/mm^3

\# High for age (16).

[In this study, patients born either vaginally (n= 15) or via elective C-section (n= 20) with proven sepsis and their healthy siblings born either vaginally (n= 20) or via elective C-section (n= 20) were included to evaluate mode of delivery effect on asthma developing. Only a few allergic infants were observed]

(Table 2, Figure 1). All atopic diseases were seen much more frequently in Group 2, namely, those children who did have neonatal sepsis and were born by elective C-section (Figure 1). Yet, probably due to the small sizes of the study groups, this finding was not statistically significant. However, adjusted risk factors for both neonatal sepsis and mode of delivery indicated no risk for asthma and other allergic diseases.

As can be seen in Table 3, for atopy rates, higher total serum IgE levels, and/or positive Phadiatop test results in Group 1 compared with Group 2 and to some degree compared with the other groups, doctor-diagnosed asthma and other diseases were almost zero (Table 3, Figure 1). Some recent studies have evaluated the relationship between neonatal sepsis and asthma prevalence. Some of these studies found a decreasing and others, an increasing, asthma prevalence with neonatal sepsis[6,7,18,19]. Of course, the inclusion and disease definition criteria of these studies were different, and none of them evaluated the effect of mode of delivery[6,7,18,19].

The studies that evaluated the influence of mode of delivery on the development of asthma were also divided in their findings; many more studies found that mode of delivery influenced the development of asthma compared with those that found mode of delivery to have no influence[8,20-27]. We think that inclusion and disease definition criteria have very important effects on the results of such studies. But because of this strict definition and inclusion criteria, the small size of the groups is the weakest aspect of this study.

In conclusion, our findings suggest mode of delivery and neonatal sepsis lend no additional risk to the development of asthma when strict inclusion and disease definition criteria are used.

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