

Effect of Neonatal Sepsis on the Development of Allergies and Asthma in Later Childhood

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Key Words

Allergic rhinitis • Asthma • Atopic dermatitis • Childhood • House dust mite • Hypersensitivity • Neonatal period

Abstract

Background: Exposure to large amounts of endotoxins and other bacterial products in early childhood may protect against the development of allergic diseases later in childhood. The aim of this study was to investigate the effects of neonatal sepsis on subsequent development of asthma, allergic rhinitis, and atopic dermatitis in children. **Methods:** We recruited 85 children (mean age 48.67 ± 12.88 months) who had been hospitalized for sepsis in their neonatal period and their siblings ($n = 85$) as controls (mean age 61.81 ± 21.34 months) to investigate the prevalences of asthma, atopic dermatitis and allergic rhinitis. After asking the questions in the International Study of Asthma and Allergies in Children (ISAAC) questionnaires to the parents, total IgE levels in sera were measured and skin prick tests were performed. **Results:** Children with neonatal sepsis had lower total IgE levels and less sensitivity to *Dermatophagoides pteronyssinus* than controls (25.9 vs. 9.4%, $p = 0.003$). In addition, wheeze ever, wheeze in the last 12 months, physician-diagnosed asthma, and use of asthma drugs were less common in these subjects. Prevalences of allergic rhinitis and atopic dermatitis were equal in both groups. **Conclusion:** Exposure

to severe infections such as sepsis in the neonatal period may decrease sensitization to environmental allergens and prevalence of asthma in later childhood.

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Introduction

The increase in the prevalence of allergic diseases, especially in industrialized countries might be due to a decreased bacterial load, thus decreased stimulation of the immune system [1]. It was suggested that bacterial infections in children at early ages attending day care centers protect these children from developing allergic reactions [2]. Similar decreases have been observed in children living on farms as a result of increased exposure to endotoxins [3]. Many cross-sectional and longitudinal studies have been performed to document the connections between childhood infections and allergic diseases [1–4]. At the end of many studies some authors have demonstrated an inverse relationship between childhood infections and atopic diseases and some others have failed [5–7]. Despite these discussions, the question of the influence of childhood infections on the development of asthma disease remains controversial. The relationship, if any, between infections and allergy in terms of time is not known precisely. However, we do know that immune responsiveness

to allergens is consolidated during the first months of life. Therefore, we may expect more protective effects of infections from allergic diseases if they are acquired in the earlier days of life [8]. On the other hand, if the assumption that early infections protect against the development of asthma and other allergic diseases is correct, then higher exposure to severe infections as early as possible, such as in the neonatal period, should protect much more than mild infections in later childhood. In this study, we aimed to investigate the prevalences of allergic diseases and asthma and hypersensitivity to some environmental allergens in children who had had sepsis in their neonatal period.

Material and Methods

The study was undertaken in Sisli Etfal Education and Research Hospital, İstanbul, Turkey. The records of neonatal intensive care unit were screened and the children who had had documented early neonatal sepsis (beginning of the sepsis symptoms in the first 7 days of life) without prematurity and any other congenital disorders were selected. The diagnosis of sepsis had been based on the symptoms of poor peripheral circulation, respiratory distress, cyanosis, lethargy, irritability, apneic spells, tachypnea, fever, bradycardia, tachycardia and poor feeding in addition to a positive blood culture [9]. After the study protocol was approved by the institutional ethics committee, the children older than two years of age and to constitute the control group one of their siblings whose ages were closest to the subjects were invited to the study. The aim of the study was described in detail to all parents and written consent was obtained. Firstly, the questions in a Turkish version of the phase one International Study of Asthma and Allergies in Children (ISAAC) questionnaire were asked to the parents. Then all of the children were examined thoroughly by a pediatric allergist for manifest findings of allergic diseases and then complete blood counting and serum total IgE measurements were made. After excluding the children in whom allergy skin testing was contraindicated due to various reasons, all children underwent skin testing with extracts of mixed extracts of certain grasses (*Poa mix*, *C. dactylon*, *P. pratensis*, *D. glomerata*, *A. sativa*, *Festuca*), trees (*Ulmus*, *Quercus*, *Populus*, *Platanus*, *Salix*), weeds (*Chenopodium*, *Artemisia*, *Plantago*, *Salsola kali*), milk, egg, *Candida albicans*, and *Dermatophagoides pteronyssinus* (Dp) (Laboratoire des Stallergenes, Fresnes Cedex, France). Skin prick tests were performed on the volar aspect of the forearm using Stallerpoint needles (Laboratoire des Stallergenes). Histamine phosphate (1 mg/ml) was used as the positive control and phosphate-buffered saline as the negative control. The cutaneous reactions were read after 15 min and evaluated according to the size of wheal and erythema. Skin prick tests were defined as positive if the mean wheal diameter was at least 3 mm larger than the negative control [10]. The skin prick tests were made by a pediatric allergist who was not aware of the results of questionnaires and IgE levels.

Statistical Analysis

Descriptive statistics were provided for the numeric and categorical variables using means, standard deviations and percent distributions where necessary. Subgroup analyses used the Mann-Whitney test to compare variables across groups, χ^2 test to compare percent distributions across levels of nominal variables and Mantel-Haenszel test to compare percent distributions across levels of ordinal variables. $p < 0.05$ was used as the cut-off for statistical significance.

Results

The study was planned for 122 children and their siblings. Unfortunately, only 85 of these children could be taken into the study because some of the parents refused joining the study or the children had no siblings. The study group aged 26–74 months (mean 48.67 ± 12.88) and 85 siblings aged 24–99 months (mean 61.81 ± 21.34) as controls ($p < 0.05$) (table 1). 58 (68.2%) of the subjects were younger and 27 (31.8%) were older than the controls. The mean birth weight of subjects was $3,190 \pm 420$ g but we could not learn the birth weights of the controls exactly, so no comparison was made in this respect. The female to male ratio was 0.8 among subjects and 0.93 among controls. The mean number of the household members was 5.33 and mean number of children in the families was 3.05. Most of the families (92%) were living in the same houses with similar conditions since the births of both of their children. None of the children had a stepparent. Maternal and paternal smoking rates were also similar during growing up in both groups of children ($p > 0.05$). Breastfeeding period of longer than 4 months was 65% among subjects and 69.4% among controls ($p > 0.05$). Gram-negative bacteria (*Escherichia coli*, *Klebsiella* species, *Serratia marcescens* and *Enterobacter* species) had grown in cultures of 29 (34.1%) subjects and Gram-positive cocci (Staphylococci and Streptococci) in cultures of 57 (65.9%) of the subjects. The neonates were given two antibiotics for at least 2 weeks during hospitalization. Wheeze ever and other signs of asthma were statistically more common among control siblings than children with neonatal sepsis (table 2) ($p < 0.05$, for each). On the contrary, allergic rhinitis and atopic dermatitis were comparable in both groups ($p > 0.05$) (table 2). Totally 13 (15.2%) of the subjects were allergic to any allergen in comparison with 28 (32.9%) of the controls ($p = 0.007$). Allergy to Dp was positive in 8 (9.4%) of the subjects and in 22 (25.9%) of the controls ($p = 0.003$). Skin tests with foods revealed positive results with egg in 4 (4.7%) of the subjects but in none of the controls and pos-

Table 1. Characteristics of children who had sepsis in the neonatal period and control siblings

	Subjects	Controls	p
Age, months	48.67 ± 12.88	61.81 ± 21.34	0.001
Female/male	38/47	41/44	0.645
Allergic parents	33/85 (38.8%)	33/85 (38.8%)	
Mothers	21/85 (24.7%)	21/85 (24.7%)	
Fathers	18/85 (21.2%)	8/85 (21.2%)	
Smoking at home	50/85 (58.8%)	0/85 (58.8%)	
4 months > breastfeeding	55 (65%)	59 (69.4%)	0.794
Weight			
<10th percentile	11 (12.9%)	2 (2.4%)	
10–90th percentile	69 (81.2%)	75 (88.2%)	
>90th percentile	5 (5.9%)	8 (9.4%)	
Height			
<10th percentile	7 (8.2%)	2 (2.4%)	
10–90th percentile	71 (83.5%)	63 (74.1%)	
>90th percentile	7 (8.2%)	20 (23.5%)	
Full childhood vaccination	81 (95.3%)	79 (93 %)	
BCG vaccination	85 (100%)	85 (100%)	
Total IgE, IU/ml	41.5 ± 49.8	67.7 ± 72.1	0.024
Higher IgE*	16 (18.8%)	29 (34.1%)	0.024

* According to the normal values for the ages.

Table 2. Prevalences of allergy symptoms in subjects and controls

	Patients (%)	Controls (%)	p
Wheeze ever	15 (17.6)	28 (32.9)	0.022
Wheeze in last 12 months	7 (8.2)	11 (13)	0.319
Exercise-induced wheeze in last 12 months	4 (4.7)	2 (2.4)	0.682
Physician-diagnosed asthma	3 (3.5)	10 (11.8)	0.043
Use of asthma drugs	11 (12.9)	23 (27.1)	0.021
Emergency room visit for acute wheezing	7 (8.2)	11 (13)	0.319
Runny nose or sneezing without a cold	15 (17.9)	15 (17.9)	1.000
Physician-diagnosed hay fever	2 (2.4)	3 (3.5)	1.000
Itchy eyes in last 12 months	0	3 (3.5)	–
Itchy rash in specific locations lasting at least 6 months in the previous year	4 (4.7)	5 (5.9)	1.000
Physician-diagnosed atopic dermatitis	2 (2.4)	1 (1.2)	–

itivity with milk in 2 (2.3%) subjects and in 5 (5.9%) of the controls. None of the subjects were allergic to pollens. Only 2 of the controls were allergic to tree pollens. Neither the subjects nor the controls were allergic to grass pollens, weed pollens or *Candida albicans*.

Discussion

The prevalence of childhood asthma and other allergic diseases have increased tremendously in the last two decades [11–13]. Although the reasons of this dramatic

increase have not yet been clarified, some important explanations and hypotheses have been proposed to account for these increases [1, 14]. The hygiene hypothesis is the most famous of these hypotheses and according to this hypothesis cumulative exposures to the food-borne and orofecal infections – such as hepatitis A – which are considered markers of poor hygiene, are inversely associated with atopy and atopic diseases [1, 15]. In our study, sepsis in neonatal life was inversely related with the development of asthma in the later years, but such a relation was not observed in the development of allergic rhinitis and atopic dermatitis.

To date, many events in neonatal period such as antenatal and postnatal exposures to allergens and head circumference at birth have been suggested to be in relation to the development of atopic diseases [16–18]. Our study demonstrates for the first time that exposure to severe infections in early neonatal period is associated with a decreased prevalence of sensitization with house dust mites and asthma symptoms in later ages. We think if there is an effect of early infections on the development of atopic diseases, this effect should be observed with more severe infections because of more exposure to endotoxins and other bacterial wall components of the responsible microorganisms. In our study group, some important signs of asthma (e.g. wheeze ever, use of asthma drugs and physician-diagnosed asthma) were less common in children with neonatal sepsis in comparison to their siblings. Since both groups have similar genetic and environmental backgrounds, decreased prevalence of asthma might be due to severe infections in early life. Although some studies have shown that indoor endotoxin exposure early in life might protect against allergen sensitization by enhancing type 1 immunity [19], some others showed that direct exposure to endotoxin is associated with increased wheezing [20] or exacerbation of asthma symptoms [21]. In our subjects, infection with Gram-positive and -negative bacteria significantly decreased allergic sensitization with house dust mites and development of asthma symptoms. We think severe neonatal infections may suppress development of asthma by producing IFN- γ and decreasing allergic sensitization [19]. In spite of many mentioned and non-mentioned studies done to investigate the relation between early life infections and development of allergies in later childhood, we still need more detailed studies to delineate the relations between asthma and infections.

Atopic dermatitis was rarely encountered among our subjects and their siblings. This has been observed both with symptoms of atopic dermatitis and doctor diagnosed atopic dermatitis. This may be due to the fact that atopic dermatitis is generally less common in our country than many other countries which has been documented in other studies [22]. The effect of the infection on the development of atopic dermatitis has been found to be greater if the first infection had occurred during the first 6 months of life [8]. Phipatanakul et al. [23] found that endotoxin levels in the home at 2–3 months of age were inversely associated with eczema in the first year of life in children with a parental history of asthma or allergies. The findings of Gehring et al. [24] also supported the hypothesis that exposure to high concentrations of endo-

toxin very early in life might protect against the development of atopic dermatitis. Our results are not in accordance with the findings of these authors. Similar to our results, Kramer et al. [25] found no protective effects of infections on atopic dermatitis or recurrent wheezing in the first 12 months of life. Some other studies reported that development of atopic dermatitis was not affected by farming activities in the environment of the children [26, 27] or infectious diseases in early childhood [28]. Briefly, the inconsistencies among the results of the studies on the relationship between asthma and infections are also evident for the relation between atopic dermatitis and infections.

Symptoms of allergic rhinitis and conjunctivitis were similar in our study and control groups. Children who had been hospitalized with salmonellosis have been reported to have lower prevalence of allergic rhinoconjunctivitis or asthma than those who had been hospitalized with nonbacterial enteritis [29]. Similarly, the prevalence of allergic rhinitis among children raised on a farm – therefore exposed to more endotoxin – has been found significantly to be lower than among their peers from the same villages who did not grow up on a farm [27]. In our study, we cannot explain exactly the reason why neonatal sepsis seems to be protective in the development of asthma but not in allergic rhinitis in spite of the concept ‘one air way, one disease’. Maybe this protective effect of sepsis on asthma development is transient, and in the long term both groups will have similar prevalences of asthma. Another plausible explanation might be that asthma and allergic rhinitis are caused by many different mechanisms and protective effects of childhood infections take place in only one of these mechanisms.

Some other factors which have been suggested to have a dampening effect on the development of allergic diseases, such as higher numbers of siblings and vaccination with BCG [30, 31] are similar in our study and control groups as well as living conditions of the houses and genetic background. On the basis of an observed inverse relationship between family size and allergic diseases, it has been proposed that exposure of young children to older children at home may protect against the development of asthma and other allergic diseases later in childhood [7, 30]. Although 31.8% of the subjects were older than the controls, in general, the control group was older than the patient group (mean age 5 vs. 4 years) in our population. Therefore, it may be argued that the main factor that protected the subjects against allergy was not neonatal sepsis, but the presence of older siblings in the household who may be responsible for exposing their

younger siblings to upper respiratory infections. However, it is well-known that although asthma symptoms develop in 80–90% of the children in the first 4–5 years of life [32], the symptoms occur in 30% of children within the first year of life and in 50% by the age 2 [33]. In addition, hypersensitivity to house-dust mite which is the most important indoor allergen in our country was significantly common among controls in our study ($p = 0.003$). Arshad et al. [34] have demonstrated that children who were skin prick-tested at 4 years were similar in most characteristics to the rest of the population and house dust mite was the most common allergen in this age. Therefore, we think that the first symptoms of asthma and hypersensitivity to house dust mite would have already appeared in the majority of our subjects if they had the risk. We could not learn the exact frequency of respiratory infections among the subjects and the controls; however, the results of studies examining the relationship between sibship size and development of allergic diseases

is still controversial [35]. In some studies, exposure to other children has been found to protect against the development of allergic diseases among children [7, 30] but in some others no association has been found [36], and some authors, such as Westergaard et al. [37] found that having siblings had been associated with a protective effect on allergic rhinitis but not on asthma. We think that the older siblings are not the decisive factor on the less frequently development of asthma and allergies to some environmental allergens among our subjects.

In conclusion, in this study we found that the children who had been hospitalized for sepsis in their neonatal period developed sensitivity to some allergens and asthma less frequently than their siblings without neonatal sepsis. It seems that neonatal sepsis might contribute to prevent the development of asthma and sensitization to some environmental allergens through some mechanisms acting on the innate immune system during its maturation.

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