

Original Article

Perinatal Risk Factors Contributing to Development of Childhood Asthma

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Abstract

Background: Genetic susceptibility and environmental factors play crucial roles in the development of childhood asthma. It seems that asthma pathology initiates in utero. The purpose of this study was to examine the relationship between various perinatal exposures and events, and the later development of childhood asthma.

Method: A total of ninety children, 45 with childhood asthma and with 45 healthy controls, referred to the Allergy Clinic of Azad University Hospitals between January 2020 and January 2021 were enrolled in the study. All caregivers or parents of these children were interviewed to collect sufficient data concerning the patients' asthma history.

Results: Gestational age, gender, low birth weight, delivery mode, maternal pre-eclampsia, maternal smoking during pregnancy, smoking exposure during the neonatal period, antibiotic prescription in the neonatal period, acetaminophen use in the neonatal period, assisted ventilation and oxygen therapy, neonatal icterus, neonatal respiratory infection, chronic pulmonary disease of prematurity, meconium aspiration, birth order as the first-born child and parental history of allergy were assessed. Among these, the use of antibiotics, oxygen therapy, respiratory infections during the neonatal period, meconium aspiration during labor, and history of allergy in first-grade relatives were the most predictable separate factors, demonstrating the key role of the perinatal period in the development of childhood asthma.

Conclusion: To conclude, although previous studies mostly suggested the causal effects of modifiable behaviors or exposures on the development of childhood asthma, the risk factors in the present study were mostly genetic influences, postnatal infections or obstetrics events or their management, which were inevitable in the process of labor.

Keywords: Childhood Asthma; Perinatal Factors; Allergy; Environmental Risk Factors

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Introduction

Asthma is the most common chronic respiratory disease in children (1) with an increasing prevalence particularly in developing countries (2). Several factors contribute to asthma development in children (3). Genetic susceptibility and environmental factors play crucial roles in the development of childhood asthma (4). It seems that asthma pathology initiates in utero and various environmental risk factors may affect the fetus in utero or neonate immediately after birth (perinatal period), which may subsequently lead to childhood asthma. Previously, perinatal stress was suggested as a leading cause of decreased CD8+ T cell function and long-term immunological consequences due to its long-life effect on the hypothalamic-pituitary-adrenal axis (5). However, because of the small number of studies the results were not convincing. Conversely, there have been some studies unable to confirm the impact of perinatal factors on the development of asthma. In these cases, only the presence of associated risk factors including atopy or maternal smoking during pregnancy may dramatically increase the risk of asthma (6).

Despite the considerable number of articles indicating the effect of risk factors in the development of childhood asthma, possible perinatal risk factors and the way they interact with the genotype inducing sensitization and later asthma development have demonstrated heterogeneous results. The purpose of this study was to examine the relationship between various perinatal exposures and events in the later development of childhood asthma in several asthmatic patients.

Materials and Methods

Study design

This cross-sectional study was performed to examine the association between perinatal factors and later development of childhood asthma. The study was conducted in Allergy clinics of Azad University Hospitals in Tehran, Iran. All caregivers or parents of the children identified with childhood asthma were interviewed to collect sufficient data concerning the patients' asthma history.

Study Population

A total of 90 children, 45 with childhood asthma

and 45 with healthy controls referred to the Allergy Clinic of Azad University Hospitals between January 2020 and January 2021 were enrolled in the study. The control group was non-asthmatic children matched with asthmatic patients in terms of age and sex. The inclusion criteria were childhood asthma in children between 4 and 14 years of age. The exclusion criteria were children having other types of allergies in addition to asthma, suffering from a systemic disease, or unwilling to participate in the study.

Statistical Analysis

For examination of the associations between perinatal factors including interacting maternal and neonatal factors among asthmatic children, the Pearson chi-squared test for two categorical variables was used.

Results

A total of 45 children between 4 and 14 years of age with childhood asthma were identified including 22 (48.9%) males and 23(51.1%) females with a mean age of 10.96±3. Meanwhile, a control group of healthy children consisting of 18 (40%) males and 27 (60%) females was also included in the study. Subsequent analyses performed on these groups did not show any significant difference regarding their age and gender. To evaluate the perinatal and early postnatal risk factors for the development of childhood asthma, we focused on the findings of previous studies and validated their effect on the patients participating in this study. Gestational age, gender, low birth weight, delivery mode, pre-eclampsia, maternal smoking during pregnancy, exposure to smoke during the neonatal period, antibiotic medications in the neonatal period, acetaminophen in the neonatal period, neonatal assisted ventilation and oxygen therapy, neonatal icterus, neonatal respiratory infection, chronic lung disease of prematurity, meconium aspiration, birth order as the first-born child and parental history of allergy were among the factors evaluated in the present study. The findings of these variables are summarized in **Table 1**.

The two variables of exposure to maternal smoking during pregnancy and the use of acetaminophen in the neonatal period were not reported in the studied group, so they were not

Table 1. A comparison of different variables studied in asthmatic cases and healthy controls.

Risk factors	Asthmatic patients 45 (%)	Healthy controls 45(%)	P-value
Preterm delivery	6 (13.3)	3(6.7)	0.485
Term delivery	39 (86.7)	42 (93.3)	0.485
Male	22 (48.9)	18 (40)	0.525
Female	23 (51.1)	27 (60)	0.525
Low Birth Weight	5 (11.1)	4 (8.9)	Non-valid
Vaginal delivery	13 (28.9)	19 (42.2)	0.271
Cesarean section	32 (71.1)	26 (57.8)	0.271
Maternal pre-eclampsia	3 (6.7)	2 (4.4)	Non-valid
Maternal smoking in pregnancy	6 (13.3)	6 (13.3)	Non-valid
Postnatal tobacco exposure	10 (22.2)	6 (13.3)	0.409
Antibiotic use in the neonatal period	7 (15.6)	0	0.012*
Use of paracetamol in the neonatal period	1 (2.2)	1 (2.2)	Non-valid
Oxygen therapy in the neonatal period	9 (20)	0	0.003*
Assisted ventilation in the neonatal period	5 (11.1)	0	0.056*
Neonatal icterus	25 (55.6)	17 (37.8)	0.139
Chronic lung disease of prematurity	3 (6.7)	0	0.242
Meconium aspiration	7 (15.6)	0	0.012*
First-born children	18 (40)	15 (33.3)	0.662
Parental history of allergy	31 (68.9)	20 (44.4)	0.033*
Breast-fed	37 (82.2)	39 (86.7)	0.672
Formula-fed	6 (13.3)	6 (13.3)	0.672

deemed to be valuable factors and therefore excluded.

Discussion

This study aimed to identify the perinatal factors that may induce the risk of asthma development. After evaluating the role of perinatal factors in the development of childhood asthma later in preschool and school years, we found a significant relationship between the use of antibiotics, oxygen therapy and respiratory infections as separate risk factors during the neonatal period, meconium aspiration during labor, and family history of allergy in first-grade relatives.

Currently, there is some evidence indicating that inflammatory mechanisms resulting from respiratory infections are detrimental to the lungs and may result in hyper-reactive airway disease. Increased apoptosis of distal airway epithelial cells and increased proliferation of endothelial and smooth muscle cells as well as several activated pathways contributing to airway remodeling

may result in stiff and fibrotic airways and hyperactivity resulting from greater smooth muscle mass (3). Apart from pneumonia and bronchiolitis as well-known predicting factors of asthma, the results of the present study also showed a significant relationship between a history of hospital admission due to respiratory infections in the neonatal period and later development of asthma in early childhood.

Although antibiotics play an important role in modern healthcare, several retrospective and prospective studies indicate that excessive antibiotic use in the early years of life may be associated with the development of asthma (7). Fong et al. recently published an article demonstrating that asthma is significantly associated with antibiotic use in children (8). Particularly, a relationship between early antibiotic exposure and gut microbiota and therefore on the hemostasis of the human immune system has been suggested. A significant positive relationship between early antibiotic exposure and later development of asthma is also

proposed in a study conducted on 2398 children, of whom 44.2% were exposed to antibiotics (9). The same results were found in the children who participated in the present study as there was a significant relationship between the use of antibiotics in their first month of life and subsequent development of asthma in their childhood.

Inspired oxygen during the neonatal period was another factor in the present study, which was identified with a meaningful relationship with the later development of asthma in the early preschool years. Previously, a retrospective cohort of 137 preterm infants receiving continuous oxygen therapy during their hospital stay was reviewed and the results showed that frequent or continuous inspired oxygen exposure during the 3 and 7 days of age in premature newborns was associated with childhood use of asthma medications (10). Although our patients were not necessarily born premature infants, many of them had received oxygen in the first days of their lives due to other reasons.

Thanks to improved perinatal care, meconium aspiration has become a rare occurrence today. It is a typical disease of term and post-term infants characterized by respiratory failure occurring in neonates born through meconium-stained amniotic fluid. Despite the significant decline in occurrence and improved survival rate of meconium aspiration syndrome over the last decades, bronchial hyper-reactivity and asthma in addition to other morbidities remain a major concern. The findings of our study were in line with the results of previous studies as a significant relationship was found between meconium aspiration syndrome and the later development of asthma. This occurrence can be explained by antenatal inflammation/infection, mechanical airway obstruction, surfactant inactivation inducing atelectasis due to meconium fatty acids and activation of the inflammatory cascade (11).

Genetic predisposition is an important predicting factor in asthma, and our results confirm that parental history of allergy and more importantly asthma are major risk factors, which may predict persistent asthma later in life. In the present study, the risk of developing asthma in children with a positive history of parental asthma was over 2.5 times greater than that of asthma development in patients without such a history.

Considering the aforementioned results, perinatal factors, specifically in association with other risk factors (e.g. atopy or maternal smoking), can be significant risk factors in the development of childhood asthma. While it is possible to control prenatal factors to a certain extent, prematurity may still occur. ICU management of the pulmonary complications of prematurity is challenging since the sequela of such management may later lead to the development of asthma. Factors such as supplemental oxygen and mechanical ventilation are the direct consequences of prematurity and may adversely affect the growing lung. Not only preterm but also term babies may experience abnormal lung function and infection leading to detrimental airway changes and remodeling. Identification of the contributing factors may allow for targeted pharmacological therapy to limit the development of asthma and its consequences. The small sample size and the fact that the study was mostly based on the parents' recall of the provocative factors were two shortcomings of the present study.

Conclusion

To conclude, among the studied perinatal factors, the use of antibiotics, oxygen therapy, respiratory infections during the neonatal period, meconium aspiration during labor, and history of allergy in first-grade relatives were the most predictable separate factors, demonstrating the key role of perinatal period in the development of childhood asthma. Although previous studies mostly suggested the causal effects of modifiable behaviors or exposures on the development of childhood asthma, the risk factors in the present study were mostly genetic influences, postnatal infections or obstetrics events as well as their management, which were inevitable in the process of labor.

Conflict of interest

Authors approve that they have no conflict of interest.

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