

The Association between Neonatal Icterus or Neonatal Phototherapy and the Likelihood of Childhood Asthma among Iranian Children

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Abstract

Background: There might be a close link between neonatal icterus and/or neonatal phototherapy and childhood asthma. The present study aimed to assess the relationship between neonatal icterus and/or phototherapy and the likelihood of childhood asthma among Iranian population.

Materials and Methods

The present case-control study was performed on 102 consecutive asthmatic children hospitalized at Children's Medical Center, Tehran, Iran. Asthma was diagnosed by a pediatric asthma and allergy specialist based on clinical manifestations and/or spirometry results for children older than 5 years. A total of 113 sex and age-matched children without asthma who were admitted to other wards during the same period of time were selected as the control group. Data were collected by a researcher-made checklist including data regarding participants' age, gender, and gestational age, history of neonatal icterus and history and duration of phototherapy, filled by participants' parents/guardians.

Results: There was a significant difference between cases and controls with respect to preterm birth, history of phototherapy and duration of phototherapy. History of icterus was not associated with childhood asthma. In the multivariable logistic regression model, both history of phototherapy ($P=0.029$), and duration of phototherapy ($P=0.03$) were considered as determinants for occurrence of childhood asthma.

Conclusion

According to the results, history of neonatal icterus was not associated with childhood asthma, but history and duration of phototherapy were both determinants of childhood asthma.

Key Words: Asthma, Childhood, Icterus, Neonate, Phototherapy.

*Please cite this article as: Mosayebi Z, Moghtaderi M, Gharib B, Gharagozlou M, Memarian S. The Association between Neonatal Icterus or Neonatal Phototherapy and the Likelihood of Childhood Asthma among Iranian Children. *Int J Pediatr* 2019; 7(3): 9133-38. DOI: [10.22038/ijp.2018.34854.3067](https://doi.org/10.22038/ijp.2018.34854.3067)

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Received date: Aug.20, 2018; Accepted date: Nov. 22, 2018

1- INTRODUCTION

According to recent reports, the overall incidence of childhood asthma has increased within the last decade (1). The upward trend in childhood asthma is not wholly explained completely explained by genetic susceptibility or changes in genetic variants and thus experts are now looking for the environmental causes of this disorder (2). Despite advances in diagnosis and treatment of asthma in children, its prevalence and the burden on the patients, their families and the health care system have risen during the past decades, and leading to increased interest in the identification of preventable risk factors of asthma (3-5). Recent evidence suggests a close link between neonatal icterus and/or neonatal phototherapy and the likelihood of childhood asthma (6-8).

It has been suggested that intracellular accumulation of unconjugated bilirubin inhibits the production of interleukin-2, leading to a T-helper type 1 (Th-1)/T-helper type 2 (Th-2) imbalance and immunoglobulin E class switch and subsequently, asthma and allergic diseases (9, 10). On the other hand, there might be a direct correlation between phototherapy for neonatal icterus with childhood asthma despite the effect of phototherapy on reduction of serum bilirubin level (11-13).

So, the association between hyperbilirubinemia, phototherapy and childhood asthma remains a matter of debate. To the best of our knowledge, only one study has been carried out to evaluate the relationship between the neonatal phototherapy and childhood asthma in Iranian children, in which the authors did not include neonates with a history of hyperbilirubinemia who had not received phototherapy (14). The present study aimed to assess the association between neonatal hyperbilirubinemia and/or phototherapy with the likelihood of childhood asthma among Iranian population.

2- MATERIALS AND METHODS

2-1. Study design and population

The present case-control study was performed on 102 consecutive children hospitalized at Children's Medical Center, a referral hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran, following an asthma attack during 2015 and 2016. Diagnosis of asthma was confirmed by a pediatric asthma and allergy specialist based on clinical manifestations and/or spirometry results for children older than 5 years. A total of 113 sex and age-matched children without asthma who were admitted to other wards during the same period of time were selected as the control group.

2-2. Inclusion and exclusion criteria

Participants were included if aged 2 to 18 years old, and had a history of neonatal icterus (either untreated or treated by phototherapy). Those who had concomitant or a history of severe medical conditions, a history of blood exchange for neonatal icterus or hospitalization during neonatal period due to medical or surgical conditions other than hyperbilirubinemia were excluded. The children in the control group were further excluded if they had a history of asthma, other atopic diseases or chronic respiratory conditions.

2-3. Ethical consideration

Informed consent was obtained from all parents at the beginning of the study and the study protocol was confirmed by the research and ethical committees at Tehran University of Medical Sciences.

2-4. Measuring tools

Data were collected by a researcher-made checklist filled by participants' parents/guardians. The checklist included data regarding participants' demographics (age, gender, gestational age), history of neonatal icterus, history, duration of phototherapy and age at the onset of

asthma, and times of hospitalization due to an asthma attack (in the case group).

2-5. Data Analysis

The analysis was performed using SPSS software (SPSS Inc, Chicago, IL, USA), version 21.0. Chi-square test was used to compare categorical variables, and Odds ratios (OR), and their 95% confidence intervals (CI) were reported. Independent sample t-test was used to compare continuous variables. Correlation between age at the onset of asthma and times of hospitalization and duration of phototherapy in children with asthma was determined by Pearson correlation and linear regression tests. To determine the predictive role of independent variables in occurrence of childhood asthma, a binary logistic regression was performed. P-values less than 0.05 were considered as statistically significant.

3- RESULTS

A total of 215 children with the average age of 6.95 ± 2.97 years (51.6% male) were recruited, of which, 102 (47.4%) were suffering from asthma, and 113 (52.6%) considering the controls. One hundred and fifty-eight (73.5%) of all participants had a history of neonatal icterus and 109 (50.7%) underwent phototherapy. Twenty-nine (13.5%) children were born prematurely. In asthmatic children, the mean age at asthma onset was 2.5 ± 1.02 years and 50% of them were hospitalized for an asthma attack at least 2 times. Comparing the two groups

with and without asthma showed no statistically significant difference regarding age and gender. However, there was a significant difference between cases and controls with respect to preterm birth (18.6% vs. 8.8%, OR=2.8, 5% CI=1.2-6.6, P-value=0.036). There was a statistically significant relationship between history of phototherapy and asthma (58.8% vs. 43.4%, OR=4.9, 95% CI=1.6-8.1, P= 0.001). Moreover, duration of phototherapy was significantly longer in children with asthma as compared to controls (2.01 ± 1.68 days vs. 1.15 ± 0.41 days, P < 0.001). In this regard, the history of icterus was slightly more revealed in asthmatic vs. non-asthmatic children (71.4% vs. 68.1%, P = 0.062) (**Table.1**).

The relationship between history of icterus with or without phototherapy and the risk for asthma was further explored after adjusting for history of preterm birth, which was considered as a confounding factor. In the multivariable logistic regression model, although history of icterus was not linked to the risk for asthma (OR = 1.803, 95% CI: 0.968–3.359, P = 0.12), both history of phototherapy (OR = 1.866, 95% CI: 1.085–3.209, P = 0.029) and duration of phototherapy (OR = 2.342, 95% CI: 1.112–3.779, P = 0.03) were main determinants for occurrence of childhood asthma (**Table.2**). In other words, the history of phototherapy and long-term phototherapy increase the risk of asthma by 1.8 and 2.3 times, respectively.

Table-1: Comparing baseline characteristics between asthmatic and non-asthmatic children

Items	Asthmatic group	Non-asthmatic group	P- value
Gender, number (%)			
Male	54 (52.9)	58 (51.3)	0.926
Female	48 (47.1)	55 (48.7)	
Age, years, mean \pm SD	7.22 ± 3.05	6.70 ± 2.90	0.196
History of preterm birth, number (%)			
Yes			0.036
No	19 (18.6) 83 (81.4)	10 (8.8) 103 (91.2)	

History of icterus, number (%)			
Yes			0.062
No	81 (71.4)	77 (68.1)	
	21 (20.6)	36 (31.9)	
History of phototherapy, number (%)			
Yes			0.001
No	60 (58.8)	49 (43.4)	
	42 (41.2)	64 (56.6)	
Duration of phototherapy, day, mean \pm SD	2.01 \pm 1.68	1.15 \pm 0.41	< 0.001

SD: Standard deviation.

Table-2: Role of independent variables in predicting childhood asthma based on multivariable logistic regression model

Variables	OR (95% CI)	P- value
History of icterus	1.803 (0.968–3.359)	0.12
History of phototherapy	4.9 (1.6-8.1)	0.001
Duration of phototherapy	2.342 (1.112–3.779)	0.03

OR: Odds ratio; CI: Confidence interval.

4- DISCUSSION

The present case-control study investigated the association between neonatal Icterus or neonatal phototherapy with the subsequent pediatric asthma among Iranian children. According to the results obtained by logistic regression analysis, history of neonatal icterus was not associated with childhood asthma, but history and duration of phototherapy were both determinants of childhood asthma. It is universally known that the immune system develops rapidly during the neonatal, infancy and early childhood; thus, many studies have attempted to investigate the main potential determinants of asthma during fetal or neonatal period when the immune system undergoes rapid development (15-17). In accordance with recent studies, the association between phototherapy and childhood asthma was shown in our case-control study (OR=4.9, 95% CI=1.6-8.1, P=0.001). Phototherapy is now globally accepted as the gold curative approach for mild to moderate neonatal icterus (18). Apart from acute complications of phototherapy including skin lesions, diarrhea, electrolyte disturbances and dehydration, it may also

lead to deleterious effects on neonatal immune system through disturbances in T lymphocytes secretion and various allergic disorders (19, 20). Theoretically, inhibition of T-lymphocyte function at the time of immune system maturation during the neonatal period may lead to decreased Th2 to Th1 lymphocyte transformation and consequently, to increased risk of childhood asthma (21). Therefore, the close link between phototherapy and the likelihood of pediatric asthma is predictable. As shown in previous studies, there is a strong association between phototherapy and various types of autoimmune diseases such as diabetes and asthma (7, 12-14, 22). In our study, the relationship between history of phototherapy and the risk for asthma was further explored after adjusting for history of preterm birth, which was considered as a confounding factor. As shown by Aspberg et al. (7) in a large Swedish population, neonatal phototherapy and/or icterus were risk determinants for children who developed asthma before the age of 12 years-old. After controlling for confounders, the odds ratio for phototherapy and/or icterus remained at 1.30 (95% CI: 1.16-1.47). In another study

by Asperg et al. (13), the association of asthma with icterus and phototherapy remained after exclusion of cases showing other neonatal risk factors and after adjustment for maternal factors (OR 1.27, 95% CI: 1.08-1.50), and increased to 1.5 if the children had been hospitalized for asthma more than once. However, some recent studies could not confirm such association so that in a study by Tham et al., no evidence was revealed for a link between phototherapy for neonatal hyperbilirubinemia and childhood allergic outcomes in a prospective mother-offspring cohort (20). Considering that phototherapy and its duration in the case group was significantly more than that in the control group, it is not clear whether the phototherapy or its duration is the risk factor in childhood asthma. Therefore, newer and further studies are necessary.

It has been made clear that bilirubin has beneficial antioxidant properties in neonates threatened by oxygen toxicity; and has a protective role against diseases triggered due to oxidant factors such as Bronchopulmonary dysplasia (BPD), retinopathy of prematurity, intra-ventricular hemorrhage and Periventricular leukomalacia (PVL) (23). Therefore, it can be inferred from the current and other recent studies that, through avoiding aggressive treatment of high but safe serum bilirubin levels, it is possible to prevent acute and long term complications of asthma and also to derive benefit from anti-oxidant traits of bilirubin in diseases induced by oxidant factors. An appropriate solution to decrease the phototherapy duration also needs to be identified. Our study had certain limitations. Since the study was of case-control type, we could not confirm a causal relationship between independent variables and childhood asthma. As with all case-control studies, there is also the risk of recall bias, i.e. individuals with a medical condition are more likely to remember previous

exposures. Moreover, we couldn't assess the relationship between neonatal serum bilirubin levels and subsequent childhood asthma. It is recommended that more studies be performed to investigate this issue.

5- CONCLUSION

Based on our results, there was an association between history of phototherapy and duration of phototherapy and asthma in children. We also found a significantly higher rate of preterm birth in asthmatic vs. non-asthmatic group. The two groups were not significantly different with regards to the history of icterus, even after adjustment for history preterm birth.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Akinbami LJ, Simon AE, Rossen LM. Changing Trends in Asthma Prevalence among Children. *Pediatrics*. 2016; 137 (1): e20152354.
2. Salam MT, Zhang Y, Begum K. Epigenetics and childhood asthma: current evidence and future research directions. *Epigenomics* 2012; 4(4): 415-29.
3. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014; 18(11): 1269–78.
4. Wu P, Feldman AS, Rosas-Salazar C, James K, Escobar G, Gebretsadik T, et al. Relative Importance and Additive Effects of Maternal and Infant Risk Factors on Childhood Asthma. *PLoS ONE* 2016; 11(3): e0151705.
5. Wen HJ, Chiang TL, Lin SJ, Guo YL. Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors. *Pediatr Allergy Immunol* 2015; 26: 272–79.
6. Huang L, Bao Y, Xu Z, Lei X, Chen Y, Zhang Y, Zhang J. Neonatal bilirubin levels and childhood asthma in the US Collaborative Perinatal Project, 1959-1965. *Am J Epidemiol*. 2013; 178(12):1691-7.

6. Aspberg S, Dahlquist G, Kahan T, Källén B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. *Pediatr Allergy Immunol*. 2010; 21(4 Pt 2): e733–e739.
7. Ku MS, Sun HL, Sheu JN, Lee HS, Yang SF, Lue KH. Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study. *Pediatr Allergy Immunol*. 2012; 23(7): 623–28.
8. Chung EK, Miller RL, Wilson MT, McGeady SJ, Culhane JF. Antenatal risk factors, cytokines and the development of atopic disease in early childhood. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92(1): F68–F73.
9. Liu Y, Li P, Lu J, Xiong W, Oger J, Tetzlaff W, Cynader M. Bilirubin possesses powerful immunomodulatory activity and suppresses experimental autoimmune encephalomyelitis. *J Immunol*. 2008; 181(3): 1887–97.
10. Saboute M, Mazouri A, Khalesi N, Hoseiny Nejad N, Razaghian A. The Effect of Intensive Phototherapy on Management of Hyperbilirubinemia in Neonates with the Gestational Age of 34 Weeks and More. *Iranian Journal of Neonatology* 2017; 8(4): 83-9.
11. Kuzniewicz MW, Niki H, Walsh EM, McCulloch CE, Newman TB. Hyperbilirubinemia, Phototherapy, and Childhood Asthma. *Pediatrics* 2018; 142 (4): e20180662.
12. Aspberg S, Dahlquist G, Kahan T, Källén B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? *Pediatr Allergy Immunol* 2007; 18(4): 313-9.
13. Mosayebi Z, Heidarzadeh M, Movahedian A, Abedi AR, Mousavi GA, Eslamian MR. The correlation between neonatal phototherapy and risk of childhood asthma in children referred to pediatric clinic of Kashan Shahid Beheshti Hospital during 2009-10. *Fez, Journal of Kashan University of Medical Sciences* 2011; 15(1): 41-6.
14. Goenkaa A, Kollmann TR. Development of immunity in early life. *Journal of Infection* 2015; 71(1): S112-S120.
15. Yavuz ST, Siebert S, Akin O, Arslan M, Civelek E, Bagci S. Perinatal risk factors for asthma in children with allergic rhinitis and grass pollen sensitization. *Allergy Asthma Proc* 2018; 39: 1–7.
16. Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedó JC. Risk and Protective Factors for Childhood Asthma: What Is the Evidence? *The Journal of Allergy and Clinical Immunology: In Practice* 2016; 4(6): 1111-22.
17. Itoh S, Okada H, Kuboi T, Kusaka T. Phototherapy for neonatal hyperbilirubinemia. *Pediatr Int*. 2017; 59(9): 959-66.
18. Xiong T, Qu Y, Cambier S, Mu D. The side effects of phototherapy for neonatal jaundice: what do we know? What should we do? *Eur J Pediatr*. 2011; 170(10): 1247-55.
19. Tham EH, Loo EXL, Goh A, Teoh OH, Yap F, Tan KH, et al. Phototherapy for neonatal hyperbilirubinemia and childhood eczema, rhinitis and wheeze. *Pediatr Neonatol*. 2018; pii: S1875-9572(17)30224-3. [Epub ahead of print]
20. Chandra S, Wingender G, Greenbaum JA, Khurana A, Gholami AM, Ganesan AP, et al. Development of Asthma in Inner-City Children: Possible Roles of MAIT Cells and Variation in the Home Environment. *J Immunol*. 2018; 200(6): 1995-2003.
21. Das RR, Naik SS. Neonatal hyperbilirubinemia and childhood allergic diseases: a systematic review. *Pediatr Allergy Immunol*. 2015; 26(1): 2-11.
22. Dani C, Martelli E, Bertini G, Pezzati M, Filippi L, Rossetti M, et al. Plasma bilirubin level and oxidative stress in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F119-23.