http:// ijp.mums.ac.ir
Original Article (Pages: 10397-10403)

Jaundiced Neonates Receiving Phototherapy and Risk of Atopic Dermatitis in the First 2 Years of Life: A Case-Control Study

Parichehr Bahraini[1], Manoochehr Karami[2], Mohammad Kazem Sabzehei[3], *Mohammad Hossein Eslamian[4]

[1]Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [2]Social Determinants of Health Research Center, Hamadan University of Medical Sciences, Hamadan, Iran. [3]Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran. [4]Clinical Research Development Unit of Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran.

Abstract

Background

Only a limited number of studies have evaluated the association between phototherapy-treated neonatal jaundice and the development of atopic dermatitis (AD) in the early childhood. In this context, the present study is aimed to assess the relationship between the AD development in the childhood and the history of phototherapy in the case of neonatal jaundice.

Materials and Methods

92 children younger than two years of age who were admitted in Besat hospital and Imam Khomeini clinic (Hamadan, Iran) were enrolled in this case-control study. The subjects were classified into the case (children with AD, n=43), and control (children without AD, n=49) groups. AD was diagnosed by an allergist according to the AD diagnostic criteria. The history of neonatal jaundice treatment with phototherapy as well as the medical records of all the recruited subjects was investigated. The data were collected by physician according to clinical manifestations and medical records. The association between phototherapy-treated jaundiced neonates and developing AD was examined.

Results

92 children were recruited. The mean age of the participants in the case and control groups was 10.56 and 9.89 months, respectively. About 74% (n=14) of the phototherapy-treated neonatal jaundice patients developed AD in their early childhood. Logistic regression analysis was used to evaluate the effect of jaundice treatment with phototherapy on the AD development in the early childhood. The prevalence of AD was higher in the patients with positive history of jaundice treatment with phototherapy ($p < 0.05$, OR=4.24, 95% CI: 1.38-13.06).

Conclusion

Based on the results, atopic dermatitis in early childhood was significantly associated with neonatal jaundice treatment by phototherapy.

Key Words: Atopic Dermatitis, Hyperbilirubinemia, Neonatal Jaundice, Phototherapy.

*Please cite this article as: Bahraini P, Karami M, Sabzehei MK, Eslamian MH. Jaundiced Neonates Receiving Phototherapy and Risk of Atopic Dermatitis in the First 2 Years of Life: A Case-Control Study. Int J Pediatr 2019; 7(11): 10397-403. DOI: **10.22038/ijp.2019.14058**

Corresponding Author:

Mohammad Hossein Eslamian (M.D), Address: Hamadan University of Medical Sciences, Ayatollah Kashani Blvd, Khajerashid cross, Hamadan, Iran.

Email: mheslamian9@gmail.com

Received date: Oct.11, 2019; Accepted date: Nov.12, 2019

1- INTRODUCTION

Atopic dermatitis (AD) is a chronic skin allergic condition characterized by pruritus and inflammation of the skin with a multifactorial etiopathogenesis which mostly occurs in children (1). Genetic, immunological and environmental factors can result in the skin barrier dysfunction and immune system dysregulation leading to AD (2). Approximately 60% of the patients develop the disease within the first year of their life and 90% of them develop it by 5 years of age (2). AD diagnosis is based on clinical symptoms, distribution pattern of the lesions and the family history of atopy (2). Children with AD have low quality of life due to itching and sleep disturbances (3, 4).

As the identification of the risk factors can help in better management of the disease, the primary objective of this study is to evaluate the association between phototherapy treatment of the neonatal jaundice and the risk of developing AD in the first 2 years of life. Neonatal Jaundice is a common condition caused by an increase in the serum bilirubin levels in which the infant's skin and sclera turn yellow due to the accumulation of bilirubin in the tissues (5). Jaundice treatment measures include phototherapy, exchange transfusion and pharmacological intervention (6). Phototherapy is widely used (6); it involves the light absorption through the skin which can convert the unconjugated bilirubin into the soluble conjugated bilirubin that can be excreted through the stool and urine (7).

Phototherapy can influence immune system and cause allergy or autoimmunity by triggering the inflammatory pathways (8). In addition studies have indicated a relationship between neonatal jaundice and development of the allergic diseases (9). The aim of this study is then the evaluation of the relationship between the childhood AD development and the history of phototherapy for the neonatal jaundice treatment.

2- MATERIALS AND METHODS

2-1. Study design and population

In order to evaluate the relationship between neonatal jaundice treatment with phototherapy and developing AD, 92 subjects were enrolled in this case-control study. The recruited participants were classified in two groups: Atopic dermatitis subjects (n=43) who referred to medical ward (also known as the case group), and the control group (n=49), subjects without AD who were admitted for other common disease (e.g. cold and diarrhea). All the recruited children were evaluated in terms of neonatal jaundice and phototherapy history. This study was conducted from August 2016 to May 2018 in two sites: Besat hospital and Imam Khomeini clinic in Hamadan, Iran.

2-2. Methods

The patient's medical record was reviewed in search for the phototherapy treatment for the neonatal jaundice. In this observational study, jaundiced neonates receiving phototherapy (Philips fluorescent lamp TL 20W/52) was considered as a predictor (independent variable), and the AD development was regarded as a dependent variable. In addition to phototherapy, the effect of gender, gestational age, type of feeding (breastfeeding, formula or both), parent's history of atopy, bilirubin level, jaundice onset day, jaundice and phototherapy duration were also investigated on the AD developing.

2-3. Laboratory measurements

AD was diagnosed by a pediatric asthma and allergy specialist according to AD diagnostic criteria. On the other hand the jaundice diagnostic criterion was the total serum bilirubin level between 14-25 mg/dL during the first 14 days of life (5).

2-4. Intervention

The usual treatment was performed for the patients in both groups without considering the study.

2-5. Ethical consideration

The study was approved by the ethics committee of Hamadan University of Medical Sciences (No. IR.UMSHA.REC.1395.358). All the patients were fully informed about the concept of the study and an informed consent form was obtained from the participants' parents.

2-6. Inclusion and exclusion criteria

The inclusion criteria were children younger than two years of age. AD diagnosis criteria included the inflammation and pruritus of skin with chronic or relapsing nature, involvement of face *and extensors and the family history of atopy (10).* Patients less than two years old with no AD who were admitted to the clinic for other common diseases such as cold and diarrheas during the same period were selected as the control group. The exclusion criteria were preterm infants born before 37 weeks of pregnancy, birth weight less than 2.5 kg and neonatal jaundice resulted from other pathologic reasons. Premature babies are more prone to jaundice than the full-term babies and those suffering from low-grade hyperbilirubinemia may receive phototherapy.

2-7. Data Analyses

Statistical analysis of data was performed by IBM SPSS software version 21.0. The normality of quantitative variables was assessed using Kolmogorov-Smirnov test. Quantitative variables were presented as mean ± standard deviation (SD). Simple logistic regression was employed to predict the effect of independent variables on the outcome variable (atopic dermatitis). This analysis was conducted in unadjusted status. Odds Ratio (OR), and 95% confidence Interval (CI) were calculated to examine the association between neonatal jaundice and AD. Prism 6.0 (GraphPad Software Inc., La Jolla, CA, USA) software was also applied for plotting the graphs. The STATA software (version 11.2) was used to determine the sample size. The statistical power of the study was considered 80%, and two-sided significant level was 0·05. Forty five subjects were estimated as the required sample size for each group (case and control).

3- RESULTS

92 subjects (51 males and 41 females) were enrolled in the study. Forty three and forty nine subjects were considered in the case and control group, respectively. All the recruited participants completed the study. The mean age of the participants in the case and control groups was 10.56 and 9.89 months, respectively. The baseline and clinical characteristics of the subjects are presented in **Table.1**. According to the results, it was found that among participants in AD group, 14 (32.6%) subjects had the history of neonatal jaundice treatment with phototherapy; 10 (23.3%) patients had the parental history of atopy (**Table.1**). Our results demonstrated that 73.7% (n=14) of the subjects with the history of phototherapy-treated neonatal jaundice developed AD in their early childhood. In addition **Figure.1** demonstrated that 39.7% (n=29) of the subjects developed AD without any history of neonatal jaundice. In the unadjusted logistic regression analysis, the phototherapy-treated neonatal jaundice and the parental history of allergy showed significant association with AD prevalence [OR=4.24, 95% CI (1.38-13.06), OR=3.4, 95% CI (0.983-11.82)], respectively (**Table.2**). This revealed that the neonatal jaundice treatment with phototherapy and parental history of allergic diseases can increase the risk of developing AD by 4.24 and 3.4 times, respectively.

Table-1: The baseline and clinical characteristics of patients in case and control groups (n=92).

Variables	Case group (Patients with AD) n=43	Control group n=49	*P*- value
Neonatal Jaundice history Number (%)	14 (32.6)	5 (10.2)	0.008
Male/Female Number (%)	26/17 (60.5/39.5)	25/24 (51/49)	0.36
Allergy history in parents Number (%)	10 (23.3)	4 (8.2)	0.04
Gestational age (day)	39.11 ± 0.95	38.83 ± 0.94	0.162
Age (Month)	10.56 ± 5.63	9.89 ± 4.53	0.528
Birth weight (kg)	3.29 ± 0.48	3.22 ± 0.42	0.428
Bilirubin (mg/dL)	16.64 ± 3.17	16.40 ± 2.07	0.877

Table-2: Logistic regression analysis of Atopic Dermatitis according to independent variables.

Variables	Dependent variables AD			
Independent variables	β	SE	*P*- value	OR 95% CI
Phototherapy in case of jaundice	1.44	0.573	0.01	4.24 1.38-13.06
Gender	0.38	0.42	0.36	1.46 0.64-3.36
Gestational age	-0.31	0.22	0.16	0.73 0.47-1.13
Feeding	-0.43	0.31	0.17	0.64 0.34-1.2
Bilirubin Level	-0.03	0.19	0.86	0.96 0.66-1.41
Jaundice onset day	-0.98	0.57	0.08	0.37 0.12-1.15
Jaundice duration	-0.34	0.88	0.7	0.71 0.12-4.05
Phototherapy duration	-0.34	0.88	0.7	0.71 0.12-4.05
Parent's history of allergy	1.226	0.634	0.05	3.4 0.98-11.82

AD: Atopic Dermatitis; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

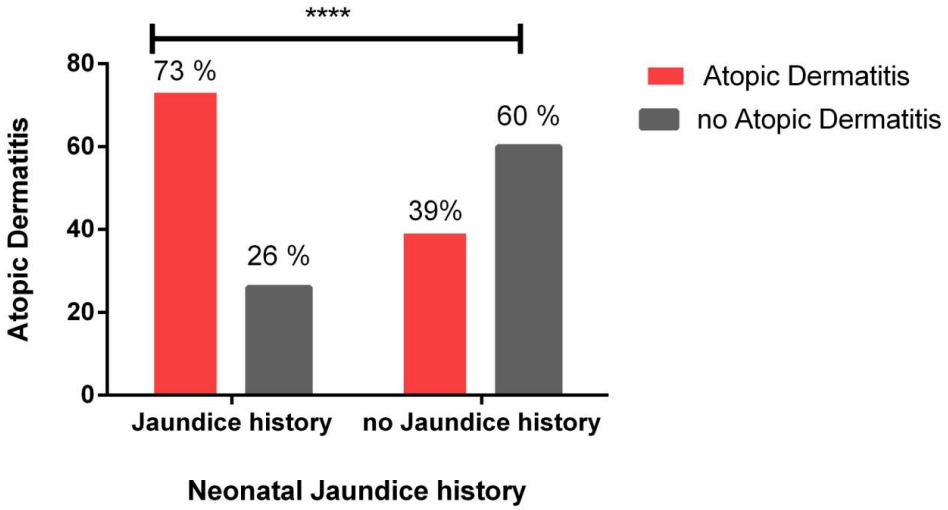

Fig.1: The relationship between AD and neonatal jaundice history.

4- DISCUSSION

The present case-control study investigated the association between neonatal jaundice managed by phototherapy and developing AD in the early childhood. The results consistently demonstrated that neonatal jaundice treatment with phototherapy increased the risk of developing AD in the first 2 years of life. Previous studies have also evaluated the association between neonatal jaundice and prevalence of allergic disorders (9, 11, 12). Phototherapy has been linked to the alterations in the immune system, which may predispose the development of atopic disorders. Bilirubin protects the infants against the oxidative stress; it also promotes the natural Th2/Th1 balance. Phototherapy interferes with this protective mechanism and disrupts the skin cytokine milieu. Phototherapy increases the production of Th2 pro-inflammatory cytokines like Tumour Necrosis Factor alpha (TNF alpha), Interleukin 1 beta (IL-1β), and Interleukin-8 (IL-8), it can also decrease Interleukin 6 (IL-6) levels, resulting in the Th2 shift towards pro-allergic tendencies (13). In addition, Kurt et al. reported that the use of phototherapy for neonatal hyperbilirubinemia influenced the cytokines production. They claimed that the serum TNF-alpha, IL-1β, IL-8 levels increased within 72 h of exposure to phototherapy (14). The results present the possible effect of phototherapy on the immune system in infants by influencing the cytokines (14). According to a study on the Iranian population by Mosayebi et.al, the history of neonatal jaundice was not associated with the childhood asthma, but the history and duration of phototherapy exhibited association with the childhood asthma (15). A similar pattern of results was obtained in a cohort study on Chinese population in which the hazardous ratios (HRs) of allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma and urticaria were higher in the neonatal jaundice cohort than the non-neonatal jaundice cohort. The HRs of the mentioned diseases was higher in the boys and those who needed phototherapy. In addition, HRs was not significantly different in the neonatal jaundice regardless of receiving the exchange transfusion (9). Another retrospective cohort study on 11,328 children under the age of 10 in Taiwan claimed that the rate of allergic rhinitis was higher in children with neonatal

jaundice. In this study, no association was found between the phototherapy and the allergic rhinitis rate (11). Another large population-based study reported that neonatal phototherapy and also neonatal jaundice seem to be associated with higher risk of hospitalization due to childhood asthma (12). A similar pattern was observed in a nationwide register-based study in Denmark on the relationship between the neonatal jaundice and the birth time in fall and winter. It was found that both increased the risk of developing AD. On the other hand, low birth weight and preterm birth were inversely associated with AD (16). In a prospective cohort study done by Huang et al., the prevalence of asthma was increased in the children at a time when phototherapy was unavailable (1956-1965) with the history of infantile hyperbilirubinemia. Total serum bilirubin levels higher than 15 mg/dL were associated with a 61% increase in the risk of developing asthma in children (17). Contrary to our findings, a recent study in Taiwan reported that UV-free light therapy in infants may prevent the allergic skin diseases for at least 5 years. They claimed the lower AD prevalence among the infants treated with icteric-phototherapy compared to those who did not received the mentioned therapy (18). The exact mechanisms underlying the effects of neonatal jaundice on allergic disorders, however, remain unclear. Some previous studies have suggested the following theories: bilirubin may inhibit Th_1 cell response. Moreover, intracellular accumulation of the unconjugated bilirubin may inhibit the production of IL-2 and thereby increase the risk of developing allergic disorders (9).

4-1. Study Limitations

The major limitation of the present study is the lack of investigation of the relationship between the AD severity and serum bilirubin level. In addition the association between jaundice cases without phototherapy treatment and developing AD was not assessed; because in practice, almost all the patients with serum bilirubin levels above 14 mg/dL were treated by the phototherapy.

5- CONCLUSION

Based on the results, this paper argued that the prevalence of AD development is higher in jaundiced neonates receiving phototherapy (as compared to the normal population). The neonatal jaundice treatment by phototherapy can be regarded as a significant predisposing factor in developing AD. However, we couldn't determine whether phototherapy or jaundice increased the risk of developing AD. Further studies with larger sample size are required to evaluate the association between phototherapy and AD development.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGEMENTS

The authors would like to thank the Clinical Research Development Unit (CRDU) of Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran for their invaluable support and cooperation throughout this study (Grant number: 9509025025).

8- REFERENCES

1. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunology and allergy clinics of North America. 2015;35(1):161-83.

2. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-51.

3. Shariati M, Nasiri Kalmarzi R, Abaei Hasani S, Goodarzi E, Hasanzadeh J, Ataee P, et al. The impact Atopic dermatitis on the life

quality of childrens 1-6 year. International Journal of Pediatrics. 2018;6(1):7003-11.

4. Vakili V, Mollazadeh Z, Ahanchian H, Kiafar B, Pedram A, Rahmani S, et al. The Impact of Infantile Atopic Dermatitis on Patients' and their Families' Quality of Life. International Journal of Pediatrics. 2019;7(6):9517-24.

5. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. British journal of hospital medicine (London, England : 2005). 2017;78(12):699-704.

6. Maisels MJ. Managing the jaundiced newborn: a persistent challenge. CMAJ : Canadian Medical Association Journal. 2015;187(5):335-43.

7. Muchowski KE. Evaluation and treatment of neonatal hyperbilirubinemia. American family physician2014;89(11):873-8.

8. Maverakis E, Miyamura Y, Bowen MP, Correa G, Ono Y, Goodarzi H. Light, including ultraviolet. Journal of autoimmunity. 2010;34(3):J247-57.

9. Wei CC, Lin CL, Shen TC, Kao CH. Neonatal jaundice and risks of childhood allergic diseases: a population-based cohort study. Pediatric research. 2015;78(2):223-30.

10. Sidbury R, Kodama S. Atopic dermatitis guidelines: Diagnosis, systemic therapy, and adjunctive care. Clinics in dermatology. 2018;36(5):648-52.

11. Sun HL, Lue KH, Ku MS. Neonatal jaundice is a risk factor for childhood allergic rhinitis: a retrospective cohort study. American journal of rhinology and allergy. 2013;27(3):192-6.

12. Aspberg S, Dahlquist G, Kahan T, Kallen B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2007;18(4):313-9.

13. Tham EH, Loo EXL, Goh A, Teoh OH, Yap F, Tan KH, et al. Phototherapy for neonatal hyperbilirubinemia and childhood eczema, rhinitis and wheeze. Pediatrics and neonatology. 2019;60(1):28-34.

14. Kurt A, Aygun AD, Kurt AN, Godekmerdan A, Akarsu S, Yilmaz E. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. Neonatology. 2009;95(3):262-6.

15. 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. International Journal of Pediatrics. 2019;7(3):9133-8.

16. Egeberg A, Andersen YM, Gislason G, Skov L, Thyssen JP. Neonatal risk factors of atopic dermatitis in Denmark - Results from a nationwide register-based study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2016;27(4):368-74.

17. Huang L, Bao Y, Xu Z, Lei X, Chen Y, Zhang Y, et al. Neonatal bilirubin levels and childhood asthma in the US Collaborative Perinatal Project, 1959-1965. American journal of epidemiology 2013;178(12):1691-7.

18. Ku MS. Neonatal Phototherapy: A Novel Therapy to Prevent Allergic Skin Disease for At Least 5 Years. Neonatology. 2018;114(3):235-41.