



## STUDY OF ATOPIC DERMATITIS RISK IN JAUNDICED NEONATES TREATED WITH PHOTOTHERAPY IN THE EARLY CHILDHOOD

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Article Received on 30/12/2019

Article Revised on 20/01/2020

Article Accepted on 09/02/2020

### ABSTRACT

Only a limited number of studies evaluated the association between phototherapy-treated neonatal jaundice and the development of atopic dermatitis (AD) in the early childhood. The present study aimed to assess the relationship between the AD development in the 1<sup>st</sup> two years of life who receive phototherapy in the case of neonatal jaundice. In this case control study, 80 children younger than two years of age who were admitted to Karama Teaching Hospital (Baghdad, Iraq) were enrolled. The subjects were classified into the case (children with AD, n=35), and control (children without AD, n=45) 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. Data were collected by a physician according to clinical manifestations and medical records. The association between phototherapy-treated jaundiced neonates and developing AD was examined. The mean age of the participants in the case and control groups was (11.6±6.6) and (10.7±5.5) months respectively. It was found that 11(68.8%) 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 = 0.01, OR=4.13, 95% CI: 1.41-10.14). Based on the results, it can be concluded that atopic dermatitis in early childhood was significantly associated with neonatal jaundice treatment by phototherapy.

**KEYWORDS:** Atopic Dermatitis, Hyperbilirubinemia, Neonatal Jaundice, Phototherapy.

### 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.<sup>[1]</sup> Genetic, immunological and environmental factors can result in the skin barrier dysfunction and immune system dysregulation leading to AD.<sup>[2]</sup> 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.<sup>[2]</sup> AD diagnosis is based on clinical symptoms, distribution pattern of the lesions and the family history of atopy.<sup>[2]</sup> Children with AD have low quality of life due to itching and sleep disturbances.<sup>[3,4]</sup> 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.<sup>[5]</sup> Jaundice treatment measures include phototherapy, exchange transfusion and pharmacological intervention.<sup>[6]</sup> Phototherapy is widely used<sup>[6]</sup>; 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.<sup>[7]</sup> Phototherapy can influence immune system and cause allergy or autoimmunity by triggering the inflammatory pathways.<sup>[8]</sup> In addition, studies have indicated a relationship between neonatal jaundice and development of the allergic diseases.<sup>[9]</sup> The aim of this study is to evaluate the relationship between the childhood AD development and the history of phototherapy for the neonatal jaundice treatment.

### MATERIALS AND METHODS

This study was conducted in Karama teaching hospital in Baghdad / Iraq during the period from August 2016 to May 2018 on (80) participants who were divided into

two groups: Atopic dermatitis subjects (n=35) who were referred to medical ward (also known as the case group), and the control group (n=45), subjects without AD who were admitted for other common diseases (e.g. cold and diarrhea). All the recruited children were evaluated in terms of neonatal jaundice and phototherapy history.

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 as well as jaundice and phototherapy duration were investigated on the AD developing.

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.<sup>[5]</sup>

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

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.

#### Data Analyses

Statistical analysis was performed by SPSS software program version 21.0. The normality of quantitative variables was assessed using Kolmogorov-Smirnov test. Quantitative variables were presented as mean  $\pm$  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.

#### RESULTS

In this study, 80 subjects (44 males and 36 females) were enrolled, and 35 and 45 subjects were considered in the case (with AD) and control (without AD) groups respectively. The mean age of the participants in the case and control groups was (11.6 $\pm$ 6.6) and (10.7 $\pm$ 5.5) months respectively. According to the results in table (1), it was found that among participants in AD group, 11 (31.4%) subjects had the history of neonatal jaundice treatment with phototherapy; 8 (22.9%) patients had the parental history of atopy. Our results demonstrated that 68.8% (11 out of 16) of the subjects with the history of phototherapy treated neonatal jaundice developed AD in their early childhood. In addition, figure (1) demonstrated that 68.6% (n=24) of the subjects developed AD without any history of neonatal jaundice; while the control group had history of phototherapy treated neonatal jaundice 11.1% (5) developed AD and 88.9% (40) did not (P=0.024).

In the unadjusted logistic regression analysis, the phototherapy-treated neonatal jaundice and the parental history of allergy showed significant association with AD prevalence [OR=4.13, 95% CI (1.41-10.14), OR=3.38, 95% CI (0.85-11.01), respectively as shown in 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 4.13 and 3.38 times respectively.

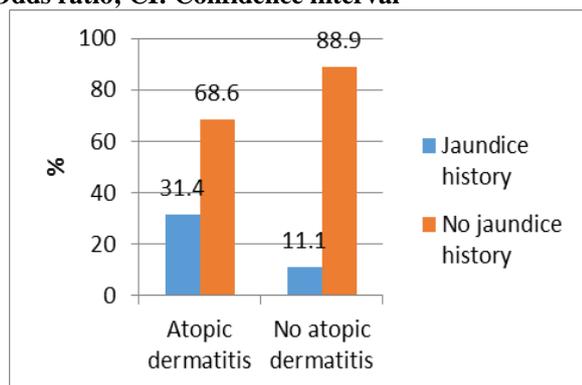
**Table 1: The baseline and clinical characteristics of patients in the case and control groups (n=80).**

Variables	AD group n=35	No AD groups n=45	P- value
Neonatal Jaundice history Number (%)	11 (31.4)	5 (11.1)	0.048
Male/Female Number (%)	19/16 (54.2/45.8)	25/20 (55.5/44.5)	0.455
Allergy history in parents Number (%)	8 (22.9)	4 (8.9)	0.041
Gestational age (day)	38.5 $\pm$ 1.05	38.8 $\pm$ 0.75	0.140
Age (Month)	11.6 $\pm$ 6.6	10.7 $\pm$ 5.5	0.508
Birth weight (kg)	3.31 $\pm$ 0.58	3.29 $\pm$ 0.49	0.868
Bilirubin (mg/dL)	16.75 $\pm$ 4.21	16.31 $\pm$ 3.15	0.594

**Table 2: Logistic regression analysis of Atopic dermatitis according to independent variables.**

Variables	Dependent variables AD			
	B	SE	P- value	OR 95% CI
Phototherapy in case of jaundice	1.39	0.569	0.01	4.13 1.41-10.14
Gender	0.40	0.39	0.46	1.51 0.95-3.41
Gestational age	-0.29	0.24	0.21	0.85 0.51-1.51
Feeding	-0.41	0.29	0.11	0.75 0.29-1.15
Bilirubin Level	-0.13	0.25	0.91	0.9 0.45-1.91
Jaundice onset day	-0.89	0.62	0.16	0.52 0.23-1.64
Jaundice duration	-0.43	0.91	0.54	0.84 0.19-4.95
Phototherapy duration	-0.41	0.75	0.65	0.95 0.19-4.15
Parent's history of allergy	1.226	0.634	0.05	3.38 0.85-11.01

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



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

## DISCUSSION

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.<sup>[9,11,12]</sup> 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 and 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-1 $\beta$ ), and Interleukin-8 (IL-8), and it can decrease Interleukin 6 (IL-6) levels, resulting in the Th2 shift towards pro-allergic tendencies.<sup>[13]</sup> 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-1 $\beta$ , IL-8 levels increased within 72 h of exposure to phototherapy.<sup>[14]</sup> The results present the possible effect of phototherapy on the immune system in infants by influencing the cytokines.<sup>[14]</sup> 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.<sup>[15]</sup> 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.<sup>[9]</sup> 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.<sup>[11]</sup> 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.<sup>[12]</sup> 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.<sup>[16]</sup> 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.<sup>[17]</sup> 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 receive the mentioned therapy.<sup>[18]</sup> 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 Th1 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.<sup>[9]</sup>

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