Chung Shan Medical Journal 2023; 34:95-102

airiti

Original Article

Confirmation of the Association Between Neonatal Jaundice and Childhood Asthma, Allergic Rhinitis, and Atopic Dermatitis

Shan-Ming Chen[1,2], Ching-Pin Lin[1,3], Min-Sho Ku[1,4]

[1] *School of Medicine, Chung Shan Medical University, Taichung City, Taiwan*

[2] *Division of Gastroenterology, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung City, Taiwan*

[3] *Division of Gastroenterology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung City, Taiwan*

[4] *Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung City, Taiwan*

Purpose: Prior investigations into the association between neonatal jaundice and asthma (AS) remain inconclusive. Furthermore, studies investigating the associations between allergic rhinitis (AR) and atopic dermatitis (AD), and neonatal jaundice are limited; most of these investigations have been database studies. Through a questionnaire-based study, we aimed to explore the association between neonatal jaundice and AS, AR, and AD.

Methods: From 12 randomly selected elementary schools in Taichung, Taiwan, 1,078 children, aged 6–8 years, were recruited. Based on the answer to a neonatal jaundice history question the children were separated into a Case Group (with neonatal jaundice history) and a Control Group (without neonatal jaundice history). Histories of doctor-diagnosed AS, AR, or AD, and other allergic conditions were also compared between the two groups.

Results: In the Case Group, the ratios of doctor-diagnosed AS (odds ratio [OR]: 2.63; 95% confidence interval [CI]: 1.85~3.73; $p < 0.001$), AR (OR: 1.89; 95% CI: 1.46~2.44; $p < 0.001$), and AD (OR: 1.90; 95% CI: 1.35~1.67; $p < 0.001$) were significantly higher than those in the Control Group. In the most recent 6 months, the incidence of airway allergy for each sex, nasal allergy for boys, and skin allergy for girls were still higher in the Case Group.

Conclusion: To the best of our knowledge, we are the first to use a questionnaire-based analysis to study the association between neonatal jaundice and allergic diseases. For children in one city in Taiwan, we found a strong association between neonatal jaundice and AS, AR, AD.

Keywords: neonatal jaundice; asthma; allergic rhinitis; atopic dermatitis

1. Introduction

Asthma (AS), allergic rhinitis (AR), and atopic dermatitis (AD) are common chronic diseases. (1). Although these allergic diseases can be effectively controlled, they are not curable. Therefore, understanding the risk factors and preventing the development of these allergic diseases is crucial. However, the causes and risk factors of these diseases are not fully understood.

Early life events or early life disease were reported

* Corresponding Author: Min-Sho Ku
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: +886-4-24739595 ext. 21728
E-mail: a129184@yahoo.com.tw

airiti

to increase the prevalence of allergic disease in later life (2, 3). Neonatal jaundice is a common problem affecting over half of all full-term and most preterm infants (4). A large cohort study, analyzing a database, found an association between neonatal phototherapy and/or neonatal icterus and the risk of hospitalization for childhood AS (5) and the prescription of anti-asthma drugs (6). The associations between neonatal jaundice, phototherapy, AS(7), AR(8), AD(9), and the usage of localized drug therapy for allergic skin disease (10) were reported by a database analysis study. Through database analyses, two large cohort studies also reported an association between AS and bilirubin levels (11-12).

However, the association between neonatal jaundice and AS is still inconclusive (13). The studies of associations between neonatal jaundice and AR or AD are relatively scarce and most of those have been database studies. Taking a new approach, through the use of a questionnaire-based study, and controlling for important confounding factors, we aimed to explore the relationship between neonatal jaundice and AS, AR, and AD in 6- to 8-year-old school-aged children.

2. Materials and methods:

2.1. Study population

In April of 2018, a questionnaire was delivered and completed for this cross-sectional survey. Twelve elementary schools in Taichung city, Taiwan were randomly selected. Children 6–8 years of age were enrolled in our study. Except for those children whose parents refused to participate, all children were included.

2.2. Questionnaire

A brief description of the symptoms and signs of AS, AR, and AD, along with airway, nasal, and skin allergies were included in the questionnaire. The questionnaire was completed by parents or guardians of the first graders, after obtaining their written informed consent. The questionnaire was modified from the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire. Children with incomplete data for analysis were also excluded from the study. The component of neonatal jaundice was determined by: Was neonatal jaundice ever mentioned (to the parents) by a doctor or nurse, in the hospital, baby care center, or clinics in the first month of age? The component of AS included: (1) Has your child ever had doctor-diagnosed AS? (2) Has your child ever had an airway allergy? (3) Has your child had any airway allergy symptoms in the last 6 months? (4) Has your child had chest wheezing that influenced their sleep at night in the last 6 months? The component of AR included: (1) Has your child ever had doctor-diagnosed AR? (2) Has your child ever had a nasal allergy? (3) Has your child had nasal allergy symptoms in the last 6 months? The component of AD included: (1) Has your child ever had doctor-diagnosed AD? (2) Has your child ever had a skin allergy? (3) Has your child had skin allergy symptoms in the last 6 months?

Questionnaires were used to determine personal and environmental factors that might affect allergic disease or neonatal jaundice. Personal factors include sex, obesity, birth type, premature birth, family history of allergic disease, and whether breastfeeding was used. Environmental factors include the number of siblings (≥ 2 or ≤ 1), parental education level (low educated: junior high school or less), second-hand smoke exposure, and having pets (cat or dog).

2.3. Association between neonatal jaundice and AS, AR, and AD

We divided the children into a Case Group (with neonatal jaundice history) and a Control Group (without neonatal jaundice history). The ratios of doctor-diagnosed AS, AR, and AD were compared between the two groups and for each sex. In addition to "doctor-diagnosed AS, AR, and AD," "airway, nasal, and skin allergy symptoms" were compared to evaluate allergic conditions noted by the parents. Then we evaluated allergic conditions in the children's lives. Allergy symptoms in the most recent 6 months were surveyed to evaluate if a history of neonatal jaundice influences the incidence of allergic disease and whether its influence on such incidence persists for 5–7 years. Chest wheezing at night was queried to evaluate neonatal jaundice history's influence on AS severity. The Institutional Review Board, Chung Shan Medical University

airiti

Hospital, Taichung, Taiwan, approved the clinical study (ethics approval number: CS16013).

2.4. Statistics

All analyses were performed using the PASW Statistics 18 software (now SPSS; IBM, Armonk, NY USA). Characteristics between the Case and Control Groups were compared using the chi-squared test. Multivariable logistic regression was used to access the associations between neonatal jaundice and AS, AR, and AD (adjusting for sex, obesity, birth type, premature birth, family history of allergy, breastfeeding, number of siblings, parental education levels, second-hand smoke exposure and having pets). Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the association. Statistical significance was set at a two-sided $p < 0.05$.

3. Results

3.1. Characteristics between the Case and Control Groups

The flow chart of the study was presented in Figure 1. After excluding those refusing to participate and those with incomplete questionnaires, 1078 children (81.5%) completed the questionnaires (boys, n = 524; girls, n = 554); 37.7% of them (n = 406; boys n = 205; girls n = 201) had neonatal jaundice as their parents recalled being informed by a doctor or nurse. Personal and environmental factor characteristics between the groups are presented in Table 1. The Case Group had a higher ratio of owning pets. Other characteristics such as family allergy history, obesity, and so on were not different between the two groups.

3.2. Association between neonatal jaundice and asthma

The results of the association between neonatal jaundice and AS are presented in Table 2. The rate of doctor-diagnosed AS was 14.1% (boys 15.5%, girls 12.8%). The ratios were significantly higher in the Case Group for all (OR: 2.63; 95% CI: 1.85~3.73; *adjusted* $p < 0.001$), for boys (OR: 2.65; 95% CI: 1.63~4.30; *adjusted* $p = 0.001$), and for girls (OR: 2.58; 95% CI: 1.56~4.28; *adjusted* $p = 0.001$). The ratios of airway allergy, airway allergy symptoms in the past 6 months, and nocturnal wheezing in the past 6 months were significantly higher in the Case Group for each sex (Table 2).

3.3. Association between neonatal jaundice and allergic rhinitis

The results of the association between neonatal jaundice and AR are presented in Table 3. The rate of doctor-diagnosed AR was 36.3% (boys 41.8%,

Table 1. Characteristics of the Case Group (with neonatal jaundice history, n=406) and the Control Group (without neonatal jaundice history, n=672)

Characteristic	Case	Control	Crude *p-value*
Sex male female	205 (39.1%) 201 (36.3%)	319 (60.9%) 353 (63.7%)	0.336
Obesity	34 (9.4%)	61 (10.5%)	0.580
Siblings ≥2	112 (27.6%)	183 (27.3%)	0.923
Family allergy	161 (39.8%)	250 (37.3%)	0.425
Cesarean birth	134 (33.1%)	241 (35.9%)	0.345
Premature birth	22 (5.4%)	23 (3.4%)	0.115
No breast milk feeding	37 (9.1%)	86 (12.8%)	0.064
Parents low education	14 (3.4%)	29 (4.3%)	0.481
Pets (dog or cat)	118 (29.1%)	150 (22.3%)	**0.013**
Second-hand smoke exposure	183 (45.2%)	288 (42.9%)	0.468

airiti

Table 2. Comparison of prevalence of AS and related conditions between the Case Group (children with neonatal jaundice history) and the Control Group (children without neonatal jaundice history)

	Case (n=406)	Control (n=672)	OR	95% CI	Adjusted *p-value**
All					
Doctor-diagnosed AS	88 (21.7%)	64 (9.5%)	2.63	1.85~3.73	**< 0.001**
Airway allergy	119 (29.3%)	95 (14.1%)	2.53	1.86~3.42	**< 0.001**
Airway allergy symptoms (past 6 months)	81 (20.0%)	68 (10.1%)	2.21	1.56~3.14	**< 0.001**
Nocturnal wheezing (past 6 moths)	36 (8.9%)	22 (3.3%)	2.88	1.67~4.96	**< 0.001**
Boys					
Doctor-diagnosed AS	48 (23.4%)	33 (10.3%)	2.65	1.63~4.30	**0.001**
Airway allergy	65 (31.7%)	48 (15.0%)	2.62	1.71~4.01	**< 0.001**
Airway allergy symptoms (past 6 moths)	47 (22.9%)	36 (11.3%)	2.34	1.45~3.76	**0.003**
Nocturnal wheezing (past 6 moths)	20 (9.8%)	10 (3.1%)	3.34	1.53~7.29	**0.005**
Girls					
Doctor-diagnosed AS	40 (19.9%)	31 (8.8%)	2.58	1.56~4.28	**0.001**
Airway allergy	54 (26.9%)	47 (13.3%)	2.39	1.54~3.71	**< 0.001**
Airway allergy symptoms (past 6 months)	34 (16.9%)	32 (9.1%)	2.042	1.22~3.43	**0.008**
Nocturnal wheezing (past 6 moths)	16 (8.0%)	12 (3.4%)	2.46	1.14~5.31	**0.008**

* Adjusted for sex, obesity, birth type, premature birth, family history of allergy, breastfeeding, number of siblings, parental education levels, second-hand smoke exposure, and having pets.
AS, asthma; OR, odds ratio; 95% CI, 95% confidence interval;

girls 31.0%). The ratios of doctor-diagnosed AR were significantly higher in Case Group for all (OR: 1.89; 95% CI: 1.46~2.44; *adjusted p < 0.001*), for boys (OR: 1.80; 95% CI: 1.26~2.67; *adjusted p = 0.006*), and for girls (OR: 1.96; 95% CI: 1.35~2.83; *adjusted p = 0.002*). The ratio of nasal allergy was significantly higher in the Case Group for each sex. But the incidence of nasal allergy symptoms in the past 6 months was not higher for girls (Table 3).

3.4. Association between neonatal jaundice and atopic dermatitis

The results of the association between neonatal jaundice and AD are presented in Table 4. The rate of doctor-diagnosed AD was 14.6% (boys 14.0%, girls 14.3%). The ratios of doctor-diagnosed AD were significantly higher in the Case Group for all (OR: 1.90; 95% CI: 1.35~1.67; *adjusted p < 0.001*), for boys (OR: 1.59; 95% CI: 0.99~2.57; *adjusted p = 0.016*), and for girls (OR: 2.26; 95% CI: 1.39~3.65; *adjusted p = 0.006*). The ratio of skin allergy was significantly higher in the Case Group for each sex. But the incidence of skin allergy symptoms in the past 6 months was not higher for boys (Table 4).

4. Discussion

Most of the previous studies investigating the

Table 3. Comparison of prevalence of AR and related conditions between the Case Group (children with neonatal jaundice history) and the Control Group (children without neonatal jaundice history)

	Case (n=406)	Control (n=672)	OR	95% CI	Adjusted *p-value**
All					
Doctor-diagnosed AR	186 (45.8%)	208 (31.0%)	1.89	1.46~2.44	**< 0.001**
Nasal allergy	219 (53.9%)	421 (37.4%)	1.96	1.53~2.52	**< 0.001**
Nasal allergic symptoms (past 6 months)	120 (29.6%)	134 (19.9%)	1.69	1.27~2.24	**0.003**
Boys					
Doctor-diagnosed AR	104 (50.7%)	116 (36.4%)	1.80	1.26~2.67	**0.006**
Nasal allergy	116 (56.6%)	139 (43.6%)	1.67	1.19~2.41	**0.010**
Nasal allergy symptoms (past 6 months)	67 (32.7%)	72 (22.6%)	1.66	1.13~2.44	**0.028**
Girls					
Doctor-diagnosed AR	82 (40.8%)	92 (26.1%)	1.96	1.35~2.83	**0.002**
Nasal allergy	103 (51.2%)	112 (31.2%)	2.26	1.58~3.23	**< 0.001**
Nasal allergy symptoms (past 6 months)	53 (26.4%)	62 (17.6%)	1.68	1.11~2.55	0.091

* Adjusted for sex, obesity, birth type, premature birth, family history of allergy, breastfeeding, number of siblings, parental education levels, second-hand smoke exposure, and having pets.
AR, allergic rhinitis; OR, odds ratio; 95% CI, 95% confidence interval;

association between neonatal jaundice and allergic disease were database analysis studies (5-9, 11-12). We used a questionnaire, with the detail of the children's history and medical conditions submitted by parents, to investigate the associations. Children with a history of neonatal jaundice (the Case Group) had 2.63, 1.89, and 1.90 times higher ratios of AS, AR, and AD, respectively, and were statistically significant after adjusting for confounders. Higher ratios of nocturnal chest wheezing in the Case Group indicated that neonatal jaundice was also associated with AS severity. Unlike the database studies, the airway, nasal, and skin allergy conditions were identified by the parents in this study. We could then understand allergic conditions in the lives of the children, as noted by the parents, rather than just using the medical records.

The increased magnitude of AS ratio was higher in our study (OR 2.63) than in two database studies in the United States (OR 1.61 in one study (11) and hazard ratio 1.04–1.30 in another study (12)) and one database study in Taiwan (7) (OR 1.64). It is difficult to compare our study to these much older studies as different study design methods, different population racial composition, and different study periods might explain some of the differences. Gau et al. (14) reported increased AS (OR: 2.72), AR (OR: 2.02), and AD (OR: 1.94) ratios in children with neonatal jaundice in Taoyuan, Taiwan. Nonetheless, in their study, only AS was significantly associated with neonatal jaundice, AR and AD were not. Our study was performed in Taichung, Taiwan. Except for climate differences between the two study areas, the other primary factors of race, economic conditions, and environmental conditions were the same in the two cities. In addition, we were unaware of their study during our study period. More study participants (1,078 children in our study and 385 children in their study) increase the power of our study.

airiti

Table 4. Comparison of prevalence of AD and related conditions between the Case Group (children with neonatal jaundice history) and the Control Group (children without neonatal jaundice history)

	Case (n=406)	Control (n=672)	OR	95% CI	Adjusted *p-value**
All					
Doctor-diagnosed AD	80 (19.7%)	77 (11.5%)	1.90	1.35~1.67	**< 0.001**
Skin allergy	108 (26.6%)	97 (14.4%)	2.15	1.48~2.92	**< 0.001**
Skin allergic symptoms (past 6 months)	39 (9.6%)	34 (5.1%)	1.99	1.23~3.20	**0.004**
Boys					
Doctor-diagnosed AD	38 (18.5%)	40 (12.5%)	1.59	0.99~2.57	**0.016**
Skin allergy	47 (22.9%)	52 (16.3%)	1.53	0.91~2.37	0.059
Skin allergic symptoms (past 6 months)	18 (8.8%)	19 (6.0%)	1.52	0.76~2.96	0.415
Girls					
Doctor-diagnosed AD	42 (20.9%)	37 (10.5%)	2.26	1.39~3.65	**0.006**
Skin allergy	61 (30.3%)	45 (12.7%)	2.98	1.93~4.60	**< 0.001**
Skin allergic symptoms (past 6 months)	21 (10.5%)	15 (4.3%)	2.62	1.32~5.21	**0.013**

* Adjusted for sex, obesity, birth type, premature birth, family history of allergy, breastfeeding, number of siblings, parental education levels, second-hand smoke exposure, and having pets.
AD, atopic dermatitis; OR, odds ratio; 95% CI, 95% confidence interval;

Some studies suggest immunological mechanisms of neonatal jaundice on allergic disease formation. First, intracellular accumulation of unconjugated bilirubin inhibits the production of interleukin-2 (IL-2) (15). A reduction in IL-2 levels skews the Th1/Th2 balance toward Th2, and Th2 has been associated with allergic disease. Hyperbilirubinemia during immune system development might predispose children to allergic conditions in later life. Second, different intestinal microflora in early life have been reported to influence the development of allergic diseases in later life (16). The amount of bile secreted into the intestine is different between icteric and non-icteric subjects and may result in different types of intestinal flora (17). Third, during hyperbilirubinemia, bilirubin enters the lung tissue and exerts a detrimental effect (18).

According to the mechanisms mentioned above, we suspect that jaundice in early life might influence the development of allergic disease and could last for an extended period. Airway, nasal, and skin allergy symptoms in the past 6 months were investigated, and the ratios were higher in AS (for each sex), AR (for boys), and AD (for girls), indicating that neonatal jaundice influences allergic disease for at least 6–8 years (Tables 2, 3, 4). The results support the speculation that jaundice in early life influences the development of allergic disease for an extended period.

Neonates with the glutathione S-transferase M1 (GSTM1) null genotype were reported to have higher total serum bilirubin (TSB) levels (19). Although the results were controversial, children with the GSTM1 null genotype were reported to be associated with AS (20-21) and AD (22). These findings suggest that gene polymorphism might be a confounder and might be the cause of AS in icteric children rather than be an effect of the bilirubin itself (12). However, in Taiwan, no association was reported between the GSTM1 null genotype and

airiti

asthma in schoolchildren (23). The ratio of AS in children with neonatal jaundice was 1.28 times (20) (pooled OR = 1.28) and 1.33 times(21) (pooled OR = 1.33) higher than those without neonatal jaundice, as reported by two meta-analysis studies. On the contrary, the increased ratio of doctor-diagnosed AS in our study was 2.63 times (OR = 2.63), and this increased magnitude was higher than the increase caused by gene polymorphism. To the best of our knowledge, the association between the GSTM1 null genotype and AR has not been reported. In our study, we found an association between AR and neonatal jaundice. Therefore, we suspect that both GSTM1 gene polymorphism and bilirubin levels might play a role in the association between neonatal jaundice and allergic disease.

In our study, we found that the incidence of nasal allergy symptoms in the past 6 months was not statistically higher for girls. In our study, we found that the incidence of skin allergy symptoms in the past 6 months and skin allergy were not statistically higher for boys. Studies indicated that the presentations and incidence for AS, AR and AD were different between genders (24). The biological difference, socio-cultural attitudes and possible differences in the threshold for seeking medical advice between genders may explain the gender difference. Gender difference may also explain the result of our study mentioned above. However, future study is necessary to find the reason.

There are strengths of our study. First, major confounders, including personal and environmental risk factors, were evaluated and adjusted for. Second, beyond the doctor-diagnosed AS, AR, and AD, airway, nasal and skin allergy factors were included in our study. We then were able to study allergic conditions in the children's lives, as noted by the parents. This may prevent the under-diagnosis of allergic disease or conditions noted by the database studies. There are some limitations to our study. First, the information was obtained from the parents' memory, and from a questionnaire. Therefore, recall bias and selection bias cannot be excluded. Second, there are no laboratory data. Third, the influence of phototherapy was not studied. No association between neonatal jaundice and allergic disease was reported by three studies (7-8, 12). Tsao et al. reported that only 8% of newborns in Taiwan accept phototherapy (25). Similar to the results reported by Tsao et al., very few children (<70 children) in our study underwent phototherapy, and with such low reliance or statistical power, investigating the effect of phototherapy is difficult. Therefore, phototherapy was not included in this study. Gathering more children who underwent phototherapy is an aim of our future research efforts.

5. Conclusion

Some studies have investigated the association between neonatal jaundice and AS. However, the association remains inconclusive to-date. We used a questionnaire-based study to investigate the association and make the association clearer. There are few prior studies that have investigated the association between neonatal jaundice and AR and AD. We found a strong association between neonatal jaundice and AR and AD. However, more studies are necessary to find the underlying biological mechanisms of this association. The results of our study indicated that, except for possible confounders such as gene polymorphism (12), neonatal jaundice itself might play a role in causing allergic disease. However, future studies are necessary to find the precise role of neonatal jaundice on allergic disease formation.

What is already known?

Prior investigations into the association between neonatal jaundice and asthma remain inconclusive. Furthermore, studies investigating the associations between allergic rhinitis and atopic dermatitis and neonatal jaundice are limited.

What this study adds?

For children in one city in Taiwan, we found a strong association between neonatal jaundice and asthma, allergic rhinitis and atopic dermatitis.

Reference:

airiti

1. Pawankar, R. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J. 2014;7:12.96.
2. Bernsen RM, van der Wouden JC, Nagelkerke NJ, de Jongste JC. Early life circumstances and atopic disorders in childhood. Clin Exp Allergy. 2006;36:858-65.
3. Codispoti CD, Bernstein DI, Levin L, et al. Early-life mold and tree sensitivity is associated with allergic eosinophilic rhinitis at 4 years of age. Ann Allergy Asthma Immunol. 2015;114:193-8.
4. Cohen SM. Jaundice in the full-term newborn Pediatr Nurs. 2006;32:202-8.
5. 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;18:313-9.
6. Aspberg S, Dahlquest G, Kahan T, Källén B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. Pediatr Allergy Immunol. 2010;21: e733-e9.
7. Ku MS, Sun HL, Sheu JN, et al. Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study. Pediatr Allergy Immunol. 2012;23:623-8.
8. Sun HL, Lue KH, Ku MS. Neonatal jaundice is a risk factor for childhood allergic rhinitis: a retrospective cohort study. Am J Rhinol Allergy. 2013;27:192-6.
9. Wei CC, Lin CL, Shen TC, Kao CH. Neonatal jaundice and risks of childhood allergic diseases: a population-based cohort study. Pediatr Res. 2015;78:223-30.
10. Ku MS. Neonatal phototherapy: a novel therapy to prevent allergic skin disease for at least 5 years. Neonatology. 2018;114:235-41.
11. Huang L, Bao Y, Xu Z, et al. Neonatal bilirubin levels and childhood asthma in the US Collaborative Perinatal Project, 1959-1965. Am J Epidemiol. 2013;178:1691-7.
12. Kuzniewicz MW, Niki H, Walsh EM, McCulloch CE, Newman TB. Hyperbilirubinemia, phototherapy, and childhood asthma. Pediatrics. 2018;142:e20180662.
13. Das RR, Naik SS. Neonatal hyperbilirubinemia and childhood allergic diseases: a systematic review. Pediatr Allergy Immunol. 2015;26:2-11.
14. Gau CC, Lee WF, Lu IC, et al. Neonatal jaundice and risk of allergic diseases by 6 years of age: a cohort study. J Allergy Clin Immunol. 2018;141:AB5.
15. Haga Y, Tempero MA, Kay D, Zetterman RK. Intracellular accumulation of unconjugated bilirubin inhibits phytohemagglutin-induced proliferation and interleukin-2 production of human lymphocytes. Dig Dis Sci. 1996;41:1468-74.
16. Björkstén B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol. 2001;108:516-20.
17. Kobayashi A, Kawai S, Ohbe Y, Benno Y. Fecal flora of infants with biliary atresia: effects of the absence of bile on fecal flora. Am J Clin Nutr. 1988;48:1211-3.
18. Dani C, Martelli E, Tronchin M, et al. Bilirubin influence on oxidative lung damage and surfactant surface tension properties. Pediatr Pulmonol. 2004;38:179-85.
19. Muslu N, Dogruer ZN, Eskandari G, et al. Are glutathione S-transferase gene polymorphisms linked to neonatal jaundice? Eur J Pediatr. 2008;167:57-61.
20. Minelli C, Granell R, Newson R. Glutathione-S-transferase genes and asthma phenotypes: human genome epidemiology (HuGE) systematic review and meta-analysis including unpublished data. Int J Epidemiol. 2010;39:539-62.
21. Piacentini S, Polimanti R, Simonelli I. Glutathione S-transferase polymorphisms, asthma susceptibility and confounding variables: a meta-analysis. Mol Biol Rep. 2013;40:3299-313.
22. Cho HR, Uhm YK, Kim HJ. Glutathione S-transferase M1 (GSTM1) polymorphism is associated with atopic dermatitis susceptibility in a Korean population. Int J Immunogenet. 2011; 38:145-50..
23. Lee YL, Hsiue TR, Lee YC, Lin YC, Guo YL. The association between glutathione S-transferase P1, M1 polymorphisms and asthma in Taiwanese schoolchildren. Chest. 2005; 128: 1156-62.
24. Osman M, Hansell AL, Simpson CR, Hollowell J, Helms PJ. Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care. Prim Care Respir J 2007;16:28-35.
25. Tsao PC, Yeh HL, Chang,YC. Outcomes of neonatal jaundice in Taiwan. Arch Dis Child 2018;103:927-9.