Assessment of Correlations Between Neonatal Jaundice and Phototherapy With Childhood Diabetes Type 1

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Abstract- Previous investigations have indicated an association between modulation of developing the immune system with increased risk of autoimmune diseases such as type 1 Diabetes Mellitus (T1DM). Objectives: In the present study, we aimed to evaluate correlations between the positive history of blood group incompatibility, neonatal jaundice, and phototherapy with childhood type 1 DM. A case-control retrospective study was carried out in an Iranian Hospital in 2015. One-hundred subjects aged 1-15 years with T1DM were included as the case group. One-hundred healthy children were also considered as the control group. A questionnaire composed of demographic-clinical data was completed for each subject. Correlations between childhood type 1diabetes and some clinical risk factors were determined. One hundred cases with type 1 diabetes and 100 healthy control children entered the study. A significant association between maternal gestational diabetes mellitus and childhood T1DM was observed (*P*=0.05, OR=3.789). The history of neonatal jaundice in the case group was significantly higher than in the control group (*P*=0.02, OR=4.667). ABO incompatibilities in the case group were associated with 19 neonates with blood group A and 2 neonates with blood group B (mothers' blood group; O) (*P*=0.005, OR=7.397). In the case group, 29 of 38 cases with a history of jaundice had received phototherapy while in the control group, 19 participants had undergone phototherapy (*P*=0.126, OR=1.707). Results have indicated that neonatal Jaundice and ABO incompatibility could increase the risk of childhood T1DM. Moreover, maternal GDM should be considered as an increased subsequent risk of childhood T1D.

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Introduction

Neonatal jaundice, with an incidence of 60-80%, is one of the most frequent problems during the early neonatal period. Although jaundice in the majority of subjects is mild and self-limiting, it is the main reason for neonate's hospitalization (1,2). Severe hyperbilirubinemia causes neurological impairment resulting in Kernicterus with short and long term morbidities (3). Jaundice is commonly treated with phototherapy preventing from reaching dangerous levels (4,5).

Former investigations have indicated an association between modulation of developing immune system in the fetal and early neonatal period with increased risk for autoimmune diseases such as type 1 Diabetes Mellitus (T1DM). It was reported that factors such as mother-infant blood group incompatibility, neonatal jaundice, and phototherapy could significantly increase the risk of childhood type 1 diabetes (1,6). It is supposed that these relevant risk factors may influence overgrowth of the pancreatic beta cells, higher autoimmunity response, and further cell death resulting in type 1 DM (7). Correlation between type 1 diabetes and phototherapy treatment may also be related to the effects of phototherapy on the neonatal gut and gut immune response (8). Another study has demonstrated a common etiology for the development of blood group incompatibility and type 1 diabetes; over-amplification of the DR3 allele was observed in both diseases (9). Although these findings were not confirmed by several investigations, no evidence of increased risk of DM-1 was observed among children who had neonatal

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hyperbilirubinemia or received phototherapy (4,10,11).

Recent studies have shown that the incidence of both neonatal jaundice and childhood type 1 diabetes is rising all around the world, especially in Asian countries (1,4,6). There are very few investigations with inconsistent findings that assessed the possible link between childhood type 1 diabetes and some risk factors related to neonatal jaundice. Therefore, in the present study, we aimed to evaluate correlations between the positive history of blood group & Rh incompatibility, neonatal jaundice, and phototherapy with childhood type 1. With further investigations in this field, we would be able to determine a new possible risk factor associated with childhood diabetes that needs tight control and observation.

Materials and Methods

A case-control retrospective study was carried out at Children's Medical Center affiliated with Tehran University of Medical Sciences (Tehran-Iran; 2015). One-hundred subjects aged 1-15 years with childhood type 1diabetes were included as the case group. One-hundred healthy children attending outpatient clinics (for check-up or vaccination) were also considered as the control group. Both groups were adjusted regarding age and sex. Children with a history of neonatal blood exchange transfusion were not included in the study.

Prior to undertaking the study, parents of the participants were invited and briefed about the purpose of the study. The related questionnaires were also presented to them. They were assured that they had the right to decline to take part in research and to withdraw from the research project at any time. All participants' parents signed informed consent. The collected data were considered confidential, and no extra cost was imposed on participants.

A questionnaire composed of demographic-clinical data was completed for each subject. Participant's age, sex, present and birth weights, height, BMI, type of delivery, type of feeding, blood group & Rh, history of neonatal jaundice, phototherapy, and risk factors related childhood type 1diabetes were collected as neonatal data. Parental ages, parents' blood group & Rh, history of diabetes in parents were also gathered and recorded in the questionnaires.

The main objective of our study was to determine correlations between childhood type 1diabetes and some clinical factors such as blood group & Rh, history of neonatal jaundice and phototherapy.

Sample size

The calculated sample size was 78 with OR=2.5. With a proposed sample size of 200 (100 in each group), our study had a power of 80% and an alpha error of 0.05.

Statistical analysis

Data from completed questionnaires were extracted, and statistical analyses were conducted using SPSS 18. Data were presented as mean±standard deviation for continuous variables and n (%) for categorical variables. Independent t-test, Chi-squared, and Bivariate Regression Analyses were used for determining the relationships between variables. *P* less than 0.05 were considered statistically significant.

The present study was taken from a medical student thesis. Our study was approved by the institutional review board of Tehran University of Medical Sciences, according to the Helsinki declaration.

Results

One hundred cases with type 1 diabetes (53 males and 47 females) and 100 healthy control children (54 males and 46 females) entered the study. The mean birth and present weights in the case and control groups were 3177±0.711 g, 28.50±11.83 Kg, and 3130±0.398 g, 27.91±11.32 Kg, respectively (*P*=0.926). The mean ages in both groups were 7.9 years. No significant differences were observed between groups regarding the sex, children and both parents' ages (*P*=0.5, *P*=0.977, *P*=0.656, *P*=0.742), respectively (Table 1).

Ten participants in the case group and 2 subjects in the control group had mothers with a history of gestational diabetes mellitus (GDM). A significant association between maternal GDM and childhood type 1 DM was observed (*P*=0.05, OR=3.789). None of the mothers had a history of type 1 diabetes, while type 2 diabetes was reported in 4 mothers (3 in the case group and 1 in the control group) (*P*>0.05). In the case group, a father had a history of type 1 diabetes. History of type 2 diabetes was also reported in 4 fathers (2 in each case and control group). However, no association was observed between the history of diabetes in fathers and their child (*P*=0.60; OR=1.005). Most of the participants in both case and control groups had blood group A^+ (45% and 41%). The history of neonatal jaundice in the case group was significantly higher than in the control group (*P*=0.02, OR=4.667). Related to mothers' blood group, A^+ was the most frequent blood group in the case group (46%) and the controls (59%). ABO incompatibility was more common in the case group compared with the

controls (21 vs. 9; *P*=0.003, OR=8.311). ABO incompatibilities in the case group were associated with 19 neonates with blood group A and 2 neonates with blood group B (mothers' blood group; O) (*P*=0.005, OR=7.397). No significant difference was observed between groups regarding Rh incompatibility (11%, 9%; *P*=0.245, OR=0.067). In the case group, 29 of 38 cases with a history of jaundice had received phototherapy while in the control group, 19 participants had undergone phototherapy (*P*=0.126, OR=1.707). There were no associations between the history of neonatal sepsis and respiratory distress syndrome with childhood type 1 DM (*P*>0.05; OR=0.523). All detailed data are shown in Table 2.

Table 1. Demographic data related to participants

Variables	Control group n=100	Case group n=100	*P*
The mean children's age (year)	7.97	7.99	0.977
Sex Male/Female	54/46	53/47	0.5
BMI (Kg/m^2)	18.42±2.99	18.47±3.06	0.724
Type of delivery Cesarean/vaginal delivery	63/37	62/38	0.5
The mean mothers' age (year)	24.94±4.16	25.51±4.52	0.743
The mean fathers' age (year)	29.40±4.26	30.56±4.93	0656

Table 2. Comparison of neonatal variables between case and control groups

Variables	Control group n=100	Case group n=100	*P*
History of jaundice	21	38	0.02
History of phototherapy	19	29	0.126
History of sepsis	4	2	>0.05
History of respiratory distress	4	2	>0.05
ABO incompatibility (O-A & O-B)	9	21	0.03
Rh incompatibility	9	11	0.245

Discussion

Former studies have illustrated positive associations between childhood diabetes type 1and some perinatal risk factors. In the present study, we investigated the possible correlation between diabetes type 1 with neonatal jaundice and phototherapy.

According to the results, there was a significant relationship between diabetes type 1 with neonatal jaundice. It is supposed that immunological responses related to jaundice may cause destructions of pancreatic β cells predisposing type 1 diabetes. Furthermore, the immaturity of the gastrointestinal tract besides poor enteral intake and delayed defecation that is involved in the etiology of neonatal jaundice may alter intestinal flora. The changes in gastrointestinal flora may initiate some inflammatory reactions resulting in damage to pancreas cells (12). Compatible to our finding, Dahlquist *et al*., have demonstrated that neonatal jaundice was a significant risk factor associated with type 1 diabetes. They concluded that this correlation was due to phototherapy treatment regardless of diagnosis (8); however, we could not confirm the role of phototherapy as an important childhood diabetes risk factor. Rami *et al*., have also indicated that a history of high bilirubin concentration and neonatal jaundice was significantly frequent among 114 cases with type 1 diabetes in comparison with 495 healthy controls (13). On the other hand, a meta-analysis study by McNamee *et al*., have indicated that of 9,520 included children with type 1 diabetes, 14% had a history of neonatal jaundice. They showed a weak association between the risk of type 1 diabetes and a history of jaundice (*P*=0.07) (6). Robertson *et al*., have also demonstrated no statistically significant association between type 1 diabetes and jaundice (10).

The results of the present study have shown that ABO incompatibilities (with OR>8), including O-A & O-B in the case group, were significantly more frequent than the control group. It seems that a common cause is involved in the etiology of both ABO incompatibility and type 1 diabetes. Berzina *et al*., have demonstrated a high frequency of the DR3 allele in both ABO immunization cases and type 1diabetes groups (9). Another investigation by Elfving *et al*., showed the increase of islet cell autoantibodies in cord blood of neonates with ABO incompatibility. By such findings, they confirmed that blood group incompatibility could be a significant risk factor for type 1 diabetes (14). Dahlquist *et al*., also illustrated a statistically significant correlation between blood group incompatibility syndromes and type 1

diabetes (8). But Waernbaum *et al*., did not observe any association between childhood type 1 diabetes and maternal-child blood-group incompatibility (15).

Based on the results, there was a significant association between mother's GDM and childhood type 1 diabetes. Compatible to our finding, Hidayat *et al*., have indicated an association between maternal gestational diabetes mellitus and increased risk of childhood T1 DM (16). Kawasaki *et al.,* also confirmed our results. They showed that intrauterine exposure to hyperglycemia could induce abnormal glucose tolerance among offspring resulting in diabetes (17).

Our study had some limitations. The present study was not a multicentre investigation to assess the role of some other regional epidemiologic factors. With a cohort study, we could evaluate the association between T1DM and phototherapy. Finally, further works with larger sample size and consideration of more neonatal risk factors are strongly suggested.

Results of the present study have indicated that neonatal Jaundice and ABO incompatibility could increase the risk of childhood type 1 diabetes. Moreover, maternal GDM should be considered as an increased subsequent risk of childhood-onset T1D**.**

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References

1. Pei-Fen L, Jeng-Dau T, Hui-Hsien P, Tung-Wei H, Hsing-Yi C, Ji-Nan S. Neonatal hyperbilirubinaemia is associated with a subsequent increased risk of childhood-onset type 1 diabetes. J Paediatr Int Child Health 2019:1-10.
2. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond) 2017; 78:699-704.
3. Sana U, Khaista R, Mehdi H. Hyperbilirubinemia in Neonates: Types, Causes, Clinical Examinations, Preventive Measures and Treatments: A Narrative Review Article. Iran J Public Health 2016;45: 558-68.
4. Amadi HO, Abdullahi RA, Mokuolu OA, Ezeanosike OB, Adesina CT, Mohammed IL6, et al. Comparative outcome of overhead and total body phototherapy for treatment of severe neonatal jaundice in Nigeria. Paediatr Int Child Health 2019;30:1-9.
5. Newman T. Wickremasinghe AC, Walsh EM, Grimes BA, McCulloch CE, Kuzniewicz MW. Phototherapy and Risk of Type 1 Diabetes. Pediatrics 2016;138: e20160687.
6. McNamee MB, Cardwell CR, Patterson CC. Neonatal jaundice is associated with a small increase in the risk of childhood type 1 diabetes: a meta-analysis of observational studies. Acta Diabetol 2012; 49:83-7.
7. D'Angeli M, Merzon E, Valbuena LF, Tirschwell D, Carolyn A.P, Mueller BA. Environmental Factors Associated With Childhood-Onset Type 1 Diabetes Mellitus An Exploration of the Hygiene and Overload Hypotheses. Arch Pediatr Adolesc Med 2010; 164:732-8.
8. Dahquist G, Llen B. Indications That Phototherapy Is a Risk Factor for Insulin-Dependent Diabetes. Diabetes Care 2003; 26:247-8.
9. Berzina L, Ludvigsson J, Sadauskaite-Kuehne V, Nelson N, Shtauvere-Brameus A, Sanjeevi CB. DR3 is associated with type 1 diabetes and blood group ABO incompatibility. Ann N Y Acad Sci 2002; 958:345-8.
10. Robertson L, Harrild K. Maternal and neonatal risk factors for childhood type 1 diabetes: a matched case-control study. BMC Public Health 2010; 10:281.
11. Stene LC, Barriga K, Norris JM, Hoffman M, Erlich HA, Eisenbarth GS, et al. Perinatal factors and development of islet autoimmunity in early childhood: the diabetes autoimmunity study in the young. Am J Epidemiol 2004; 160:3-10.
12. Lisu H, Yixiao B, Zongli X, Xiaoping L, Yan C, Yongjun Z, et al. Neonatal Bilirubin Levels and Childhood Asthma in the US Collaborative Perinatal Project, 1959-1965. Am J Epidemiol 2013; 178:1691-7.
13. Rami á U. Schneider á A. Imhof á T. WaldhoÈr á E. Schober. Risk factors for type I diabetes mellitus in children in Austria. Eur J Pediatr 1999; 158:362-6.
14. Elfving AM, Lindberg BA, Landin-Olsson M, Hampe CS, Lernmark A, Ivarsson SA. Islet cell autoantibodies in cord blood from children with blood groupincompatibility or hyperbilirubinemia. Autoimmunity 2003; 36:111-5.
15. Waernbaum I, Dahlquist G2, Lind T. Perinatal risk factors for type 1 diabetes revisited: a population-based register study. Diabetologia 2019; 62:1173-84.
16. Hidayat K, Zou SY, Shi BM. The influence of maternal body mass index, maternal diabetes mellitus, and maternal smoking during pregnancy on the risk of childhood-onset type 1 diabetes mellitus in the offspring: Systematic review and meta-analysis of observational studies. Obes Rev 2019; 20:1106-20.
17. Kawasaki M, Arata N, Ogawa Y. Obesity and abnormal glucose tolerance in the offspring of mothers withdiabetes. Curr Opin Obstet Gynecol 2018;30:361-8.