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Risk Factors for Type 1 Diabetes Mellitus among Children and Adolescents in Basrah

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Abstract

Objectives: Environmental factors play an important role in the pathogenesis of type 1 diabetes mellitus, many of these factors have been uncovered despite much research. A case-control study was carried out to determine the potential maternal, neonatal and early childhood risk factors for type 1 diabetes mellitus in children and adolescents in Basrah.

Methods: A total of 96 diabetic patients who have been admitted to the pediatric wards at 3 main hospitals in Basrah, and those who have visited primary health care centers over the period from the 4th of November 2006 to the end of May 2007 were recruited. In addition, 299 non-diabetic children were included, their age ranged from 18 months to 17 years.

Results: Family history of type 1 diabetes mellitus and thyroid diseases in first and second degree relatives was found to be an independent risk factor for type 1 diabetes mellitus, (p<0.001). Regarding maternal habits and illnesses during pregnancy, the study has revealed that tea drinking during pregnancy is a risk factor for type 1 diabetes mellitus in their offspring, (p<0.05). In addition, maternal pre-eclampsia and infections were found to be significant risk factor for type 1 diabetes mellitus, (p<0.001). Neonatal infections, eczema and rhinitis during infancy were also significantly associated with development of type 1 diabetes mellitus. Moreover, the results revealed that duration of <6 months breast feeding is an important trigger of type 1 diabetes mellitus.

Conclusion: Exposure to environmental risk factors during pregnancy (tea drinking, pre-eclampsia, and infectious diseases), neonatal period (respiratory distress, jaundice and infections) and early infancy are thought to play an important role in triggering the immune process leading to B-cell destruction and the development of type 1 diabetes mellitus.

Keywords: Type 1 Diabetes Mellitus; Risk factors; Children; Adolescents.

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Introduction

Type 1 diabetes mellitus (T1DM), a chronic autoimmune disease, is thought to be triggered by as yet unidentified environmental factors in genetically susceptible individuals, the major genetic contribution coming from loci within the HLA complex, in particular HLA class II.[1]

Despite recent progress in understanding the genetics and immunology of the disease, its incidence continues to increase by 3-5% per year. The high and increasing incidence, associated severe morbidity, mortality and enormous health care expenditures, makes T1DM a prime target for prevention.[2]

The etiology of type 1 diabetes is uncertain,[3] environmental triggers such as certain dietary factors and viruses are thought to initiate the autoimmune process, leading to the destruction of pancreatic B-cell and consequent T1DM. A genetic predisposition is another pre-requisite, allowing the autoimmune process to progress.[4,5]

Environmental factors playing a role in the pathogenesis of T1DM may differ substantially from population to population. More specifically, disease incidence in one geographical area may differ from another because of different exposures to a given risk factor or because of difference between population genetic susceptibilities to that risk factor.[6]

Although the etiologic role of viral infections in human T1DM is controversial; coxsackie B_3, coxsackie B_4, cytomegalovirus, rubella, and mumps can infect human B cells.[4,7,8]

The mechanisms of action of different nutritional constituents that may play a role in the development of B cells autoimmunity are largely unknown. It also remains to be defined whether these exposures, or lack thereof initiate B cell autoimmunity or promote or accelerate an ongoing process.[9,10]

Disproportionate maternal influences on the risk of T1DM suggests that critical disease-inducing environmental events operate very early, even in the utero. A number of maternal-related events are associated with an increased disease risk in children but not in adults.[11]

The aim of disease prediction is disease prevention. T1DM could be prevented by avoiding those environmental factors that cause the disease process (primary prevention) or modulating the destructive process before the onset of clinical diabetes (secondary prevention).[11,12]

This case- control study was carried out to assess maternal factors that are potentially involved in the development of T1DM, and explore the contribution of neonatal and early childhood factors on the risk of T1DM development.

Methods

A case-control study carried out on children and adolescents with T1DM and non-diabetic children over the period from the 4th of November 2006 to the end of May 2007. Children and adolescents with T1DM who have been admitted to pediatric wards at Basrah Maternity and Children Hospital, Basrah General Hospital, Port Hospital and those who have visited two Primary Health Centers in the center of Basrah were recruited for this study. A total of 96 diabetic patients, (age range: 18 months - 17 years) were included in the study. Sample size was determined by the availability of patients and time span of the study.

The control group included 299 non-diabetic children and adolescents who were randomly selected from children consulting the outpatient department of Basrah Maternity and Children Hospital, primary Health center for minor illnesses or accompanying their parents during the visit were included in the study, their age ranged from 18 months - 17 years. There are no ethnic subgroups in Basrah; the population is generally homogenous (Arab Muslims).

A special questionnaire was designed for the purpose of the study. The following information were taken; name, age, sex, age at diagnosis (for diabetic patients only), family history of DM: T1DM or type 2 diabetes (T2DM), family history of other autoimmune diseases (celiac disease, thyroid disease, pernicious anemia, vitiligo) in the first and second degree relatives. Decimal age was calculated using the decimal calendar.[13]

Maternal factors included; maternal habits (smoking, coffee, tea), while maternal diseases included pre-eclampsia, gestational DM, autoimmune diseases, and infectious diseases (e.g., fever, diarrhea, skin rash, etc). In addition, history of drug ingestion during pregnancy was assessed, including the use of antibiotics, analgesics, antihypertensive, anti-emetic, steroidal and non-steroidal anti-inflammatory drugs, anti-epileptic drugs, and insulin for diabetes. Tea quantification was done on 2 stages; a) whether they drink tea or not, and b) if they drink tea, how many cups/day using the unified Iraqi tea cup (Istikana).

Potential neonatal risk factors included the place of delivery (hospital or home), mode of delivery (vaginal delivery or cesarean section) and gestational age at birth (pre-term or full term). In addition, diseases during neonatal period were recorded including; respiratory distress syndrome, jaundice, and infections.

History of infectious diseases during early childhood; rubella, measles, varicella, pertussis, mumps, autoimmune diseases like celiac disease, in addition to history of rhinitis and asthma were also recorded. Data regarding possible risk factors in early infancy were also assessed, such as conjunctivitis and eczema for all children recruited in the study.

The questionnaire also included the type of feeding in early life (breast feeding, formula milk feeding) and its duration. Informed consent was obtained from one or both parents and/older children and adolescents, for recruitment in the study.

Statistical analysis was done using SPSS program, data were expressed and comparisons of proportions was performed using chi square, $p<0.05$ was considered as statistically significant. Logistic regression analysis was also done for the analysis of different potential risk factors, for each variable the odd ratio (OR) and 95% confidence interval (CI) were assessed.

Results

A total of 96 children and adolescents with type 1 diabetes and 299 non-diabetic children were included in this study. There is no statistically significant difference concerning the age and sex distribution between diabetic patients and control group ($p>0.05$). (Table 1)

Table 1: Distribution of cases and control group according to age and sex

Decimal Age (years)	Cases No. (%)	Control No. (%)	*p* value
1.201 - 4.96	10 (10.4)	31 (10.3)	>0.05
5.124 - 8.908	39 (40.7)	108 (35.4)	
9.1 -13.92	42 (43.7)	121 (40.4)	
14.21 - 17.102	5 (5.2)	39 (13.9)	
Sex			
Male	33 (34.4)	99 (33.2)	>0.05
Female	63 (65.6)	200 (66.8)	
Total	**96**	**299**	

All children and adolescents included in the study were assessed in terms of family history of T1DM, T2DM and family history of other autoimmune diseases like celiac disease, thyroid disease, and vitiligo, the results are presented in Table 2. It was found that diabetic patients have a statistically significant positive family history of T1DM, or both T1DM and T2DM. However, a positive family history of T2DM was reported in a significantly higher number of children in the control group.

Table 2 also clearly demonstrates that most children in the control group (91.2%) have no family history of autoimmune diseases other than DM. In contrast, the frequency of these autoimmune diseases was significantly higher among diabetic patients ($p<0.01$), including thyroid disease, celiac disease and vitiligo.

When considering potential risk factors during pregnancy, a significantly higher number of mothers in the control group had no particular dietary habits, no specific maternal diseases or medications intake during pregnancy. Drinking tea was reported in a significantly higher number of mothers of diabetic children compared to mothers in the control group. (Table 3)

Table 2: Family history of autoimmune diseases among patients and controls

Family history of autoimmune diseases	Cases No. (%)	Control No. (%)	*p* value
Family history of DM *			
No	40 (41.7)	189 (63.2)	<0.01
T1DM	26 (27.1)	3 (1.0)	
T2DM	20 (20.8)	107 (35.8)	
T1DM + T2DM	10 (10.4)	0 0	
Family history of other autoimmune diseases *			
No	71 (74.0)	273 (91.2)	<0.01
Celiac disease	3 (3.1)	0 0	
Thyroid disease	15 (15.6)	10 (3.4)	
Vitiligo	7 (7.3)	16 (5.4)	
Total	**96**	**299**	

**p-value was assessed between two groups (those with negative and positive family history).*

Table 3: Potential risk factors during pregnancy of the index child

Risk factor	Cases No. (%)	Control No. (%)	*p* value
Maternal habits			
No	10 (10.4)	105 (35.2)	<0.001
Coffee	2 (2.1)	7 (2.3)	
Tea	84 (87.5)	187 (62.5)	
Maternal diseases			
No	54 (56.2)	256 (85.3)	<0.001
Pre-eclampsia	17 (17.7)	20 (7.0)	
Gest. DM	11 (11.5)	5 (1.7)	
Infectious diseases	14 (14.6)	18 (6.0)	
Maternal drugs			
No	48 (50.0)	208 (69.6)	<0.01
Antibiotics	9 (9.4)	20 (6.7)	
Analgesics	5 (5.2)	13 (4.3)	
Antihypertensive	13 (13.5)	4 (1.3)	
Anti-emetic	18 (18.8)	49 (16.4)	
Anti-epileptic	0 0	2 (0.7)	
Insulin	3 (3.1)	3 (1.0)	

The study revealed also that a significantly higher number of mothers in the control group (85.3%) were free from diseases, compared to mothers of diabetic children (56.2%), $p<0.001$. Pre-eclampsia, gestational diabetes and infectious diseases were reported in significantly higher frequency of mothers of diabetic children.

For maternal drug intake during pregnancy, a significantly higher number of mothers in the control group (69.6%) were not taking drugs during pregnancy. While, a significantly higher number of mothers of the diabetic children reported a history of antihypertensive intake, as well as antibiotics, analgesics and anti-emetics during pregnancy, ($p<0.01$).

However, none of the mothers in either group was a smoker, or reported a history of autoimmune diseases, intake of anti-epileptic drugs, or steroidal and non-steroidal anti-inflammatory drugs during pregnancy.

Potential neonatal risk factors that were assessed included mode and place of delivery (hospital, home, vaginal delivery, cesarean section) and neonatal diseases including (respiratory distress, jaundice and infection), as shown in Table 4. A significantly higher number of mothers in the control group (38.8%) had delivered the index child by normal vaginal delivery at home. While a significantly higher number of cases were delivered by cesarean section ($p<0.01$).

Table 4: Neonatal risk factors

Risk factor	Cases No. (%)	Control No. (%)	*p* value
Place and mode of delivery			
Hospital			
NVD	64 (66.7)	170 (56.9)	<0.01
C/S	15 (15.6)	13 (4.3)	
Home: NVD	17 (17.7)	116 (38.8)	
Neonatal diseases			
No	34 (35.4)	199 (66.6)	<0.01
Respiratory diseases	22 (22.9)	18 (6.0)	
Jaundice	29 (30.2)	80 (26.8)	
Infection	11 (11.5)	2 (0.7)	

NVD: Normal Vaginal Delivery
C/S: cesarean section

For neonatal diseases, a significantly higher number of children in the control group (66.6%) had no history of neonatal diseases, compared with diabetic children who had a statistically significant association of respiratory distress, jaundice and infectious diseases, ($p<0.01$).

There was no statistically significant difference regarding gestational age at birth between the study group and the control group.

Potential environmental factors that have occurred during early life including infectious diseases and other diseases were also assessed, (Table 5). This table demonstrates that a significantly higher number of children in the control group (86.3%) have no history of infectious diseases in comparison with diabetic patients. Measles, varicella, pertussis and mumps were reported in a significantly higher number of diabetic patients compared to control group. None of children in both groups gave a history suggestive of rubella.

Most of the children in the control group (81.3%) were breast fed for more than 6 months compared to the diabetic children (57.3%), the difference was statistically significant, ($p<0.01$). Introduction of weaning foods before the age of 6 months was significantly higher among diabetic patients compared to the control group, ($p<0.01$). (Table 6)

In terms of independent variables showing significant

association with T1DM; the whole variables included in the study were subjected to logistic regression analysis to adjust the possible confounders to determine the variables which are associated with T1DM, (Table 7). Significant risk factors for the development of T1DM were; family history of T1DM and of thyroid disease in first and second degree relatives, maternal tea drinking, maternal pre-eclampsia, neonatal infections, measles and varicella in early childhood, rhinitis and eczema.

Table 5: Environmental factors during early life among patients and controls

Risk factor	Cases No. (%)	Control No. (%)	*p* value
Infections			
No	62 (64.6)	258 (86.3)	<0.01
Measles	13 (13.5)	14 (4.7)	
Varicella	13 (13.5)	21 (7)	
Pertussis	6 (6.3)	2 (0.7)	
Mumps	2 (2.1)	4 (1.3)	
Diseases			
No	48 (50)	243 (81.4)	<0.01
Thyroid disease	2 (2.1)	1 (0.3)	
Celiac disease *	0 0	1 (0.3)	
Rhinitis	25 (26)	26 (8.7)	
Conjunctivitis	6 (6.3)	9 (3)	
Asthma	7 (7.3)	9 (3)	
Eczema	8 (8.3)	10 (3.3)	

** p-value was not assessed for celiac disease*

Table 6: Nutritional risk factors among cases and controls

Feeding pattern	Cases No. (%)	Control No. (%)	*p* value
Duration of Breast feeding			
<6 months	10 (10.4)	2 (0.67)	<0.01
>6 months	55 (57.3)	243 (81.3)	
Total	**65 (67.7)**	**245 (81.9)**	
Time of introduction of weaning foods			
<6 months	61 (63.5)	120 (40.2)	<0.01
>6 months	35 (36.5)	179 (59.8)	
Total	**96 (100)**	**299 (100)**	

Table 7: Logistic regression analysis

Risk factor	X^2	*p* value	OR	95%CI
Family history of T1DM	217.95	<0.001	$5.8E^{-08}$	$6.35E^{-09}$ - $5.3E^{-07}$
Family history of thyroid disease	29.146	<0.001	0.08	0.0017 - 0.44
Maternal habit (tea)	11.8	<0.05	4.66	1.36 - 16.05
Maternal pre-eclampsia	43.699	<0.001	$8.6E^{+07}$	$3.3E^{+07}$ - $2.3E^{+08}$
Neonatal infection	27.648	<0.001	0.06	0.002 - 1.3
Diseases in early life				
Measles	13.667	<0.05	$7.79E^{-09}$	$1.2E^{-09}$ - $5.0E^{-08}$
Varicella	13.067	<0.05	$1.36E^{-08}$	$2.18E^{-09}$ - $8.5\ E^{-08}$
Rhinitis	48.75	<0.001	5.25	1.725 - 15.982
Eczema	48.76	<0.001	3.75	1.3 - 14.02

Discussion

This case-control study is the first study describing the risk factors for T1DM in Basrah. The aim of this study was to analyze the environmental factors that predispose to type 1 diabetes in children.

In this study, the risk of T1DM was significantly associated with the occurrence of T1DM (either alone or in addition to family history of T2DM) in first and second degree relatives. This finding is similar to that reported by Sipetic et al. in Yugoslavia,[14] Wahlberg et al. in Sweden[15] and Moussa et al. in Kuwait.[16] In contrast, a family history of T2DM did not influence the risk, this result is consistent to that reported by Eltobelli et al. in Italy.[17]

T1DM and T2DM frequently co-occur in the same family, suggesting common genetic susceptibility. Such mixed family history is associated with intermediate phenotype of diabetes; insulin resistance and cardiovascular complications in T1DM, lower BMI and less cardiovascular complications in T2DM.[18]

Concerning family history of other autoimmune diseases, the study showed that there was a statistically significant association of occurrence of thyroid disease among relatives of diabetic patients compared to non-diabetic children and adolescents, similar results was reported by Moussa et al. in Kuwait.[16] T1DM and autoimmune thyroid disease are the most common autoimmune endocrine disorders. A common genetic factor was suggested because of similar pathogenesis and tendency to occur together. HLA-DR3 was the major HLA allele contributing to the genetic susceptibility to TIDM and autoimmune thyroid disease.[19] In addition, CTLA-4 + 49 A/G and CT60 gene polymorphism was found to confer genetic susceptibility to type 1 diabetes, particularly in patients with thyroid autoimmunity.[20]

Maternal smoking was not reported among mothers of diabetic or non-diabetic children. Drinking tea by mothers during pregnancy was significantly associated with T1DM, a similar result was reported by Visalli et al. in Italy.[6] Among maternal diseases, this study showed a significant correlation of T1DM with maternal pre-eclampsia, and infections among mothers of diabetic patients, similar results were found by Dahlquist et al. in a study which included 7 centers in Europe,[21] and Stene et al. in Denver.[22] Algert et al. reported that pre-eclampsia was significantly associated with childhood diabetes, but only among children diagnosed before 3 years of age.[23] Complications during pregnancy have been related to affect the fetal immune system, although the mechanisms are not known. Maternal diabetes either pre-gestational or gestational, is associated with an increased risk of a number of pregnancy related complications.[22] In contrast, a study in Norway by Stene LC et al. [24] has concluded that maternal pre-eclampsia, perinatal infections and cesarean section were not significantly associated with the incidence of T1DM in children.

Maternal infection during pregnancy are among the important environmental triggers of T1DM, a similar result was reported by Dahlquist et al. in Sweden.[25] Certain enteroviruses or rotavirus during fetal life or infancy may be associated with B-cell autoimmunity and the development of clinical T1DM.[9]

Potential neonatal risk factors have confirmed a significant association between infections, respiratory distress and jaundice in neonates and T1DM. Similar results were obtained by Dahlquist et al. in Europe,[21] and by Mc Kinney et al. in the UK,[26] who reported that neonatal respiratory diseases, infections and jaundice are risk factors for T1DM. The most impressive increase in jaundice as a risk factor for T1DM was that found for blood group incompatibility, specifically ABO incompatibility, hence the mechanism is unknown.[21] Dahlquist et al. in Sweden,[27] have also reported that jaundice at birth or soon after birth has shown to be associated with increased risk of T1DM and it has been suggested that this association is due to phototherapy that these children have received. Neonatal infections were significantly associated with T1DM in this study, this result is consistent with that reported by Svensson et al. in Denmark.[28]

A more recent study in Scotland did not reveal a significant association between type 1 diabetes and maternal pre-eclampsia, mode of delivery, jaundice, phototherapy, or breast feeding.[29] Early childhood infections were reported in a significantly higher percent of diabetic children compared to the control group. History of measles and varicella attend significant association with T1DM, similar results were reported by Bengt et al. in Sweden.[30] Data from experimental animals as well as in vitro studies indicate that various viruses are clearly able to modulate the development of T1DM via different mechanisms including direct B-cell lysis, by activation of auto-reactive T-cell, loss of regulatory T-cell and molecular mimicry.[31]

However, Cardwell et al. reported a significant reduction in the risk of diabetes in children who lived with more siblings compared with one or none, and in children who moved house more often compared with never. The reduced risk of type 1 diabetes in children living with siblings, sharing a bedroom and moving house more often could reflect the protection afforded by exposure to infections in early life and consequently may provide support for the hygiene hypothesis.[32]

The hygiene hypothesis postulates that early environmental stimulation by infections is necessary for mature and balanced immune responses. The protective mechanisms induced by infection are thought to be related to the production of regulatory T-cells. Complex interactions between various components of the immune system control the production of Th1 cells, which are associated with autoimmune disease, and Th2 cells, which are associated with allergic disease. Such interactions could explain an inverse relationship between autoimmune and allergic disease such that the hygiene hypothesis is consistent with an inverse association between atopic diseases and type 1 diabetes.[33]

Eczema and rhinitis in early life were significantly associated with T1DM in this study, similar results were obtained by Visalli et al. in Italy, [6] and Sipetic et al. in Yugoslavia.[14]

Atopic eczema (AE) is one of the most frequent chronic inflammatory skin diseases due to complex interactions of deficient innate and adaptive immune responses based on a strong genetic predisposition and triggered by environmental factors. AE patients exhibit a higher tissue eosinophilia, enhanced lesional cytokine expression, and higher surface expression of the high-affinity receptor for IgE (FcεRI) on epidermal dendritic cells compared to non-atopic eczema patients.[34]

In contrast to the Norwegian Children Diabetic Study Group by Stene et al. which showed that atopic eczema was associated with lower risk of T1DM, suggesting that it may confer partial protection against T1DM.[35] A weak inverse association between diabetes and each atopic exposure was also concluded from the meta-analysis of published literature, although none attained statistical significance.[33] The observed inverse association between childhood eczema and type 1 diabetes is not likely to be explained by the established diabetes susceptibility genes HLA-DQ, CTLA4, or PTPN22.[36]

Feeding pattern in early life (breast, cow milk or mixed feeding) and its duration were assessed in this study and showed that breast feeding less than 6 months is an important factor among diabetic children. Similar results were reported by Visalli et al. in Italy,[6] and by Holmberg et al. in Sweden who concluded that breast feeding modifies the risk of beta cells autoimmunity even years after finishing breast feeding.[37] However, Micheal et al. in Germany,[38] and Couper et al. in Australia,[39] did not confirm the role of the duration of the breast feeding or the introduction of cow's milk feeding as a risk factor for T1DM.

Accumulated evidence supports a critical role of environmental factors in its development. Prospective birth cohort studies show that the first signs of beta cell autoimmunity may be initiated during the first year of life. This implies that risk factors for beta cell autoimmunity and type 1 diabetes must be operative in infancy. Early nutrition provides essential exogenous exposures

in that period. Most studies suggest that the early introduction of complex foreign proteins may be a risk factor for beta cell autoimmunity.[40]

The main limitation of the study was the limited time of the study which limited the number of diabetic patients enrolled in the study.

Conclusion

From this study it can be concluded that exposure to environmental risk factors during the neonatal period (respiratory distress, jaundice and infections) and the first years of life is thought to play an important role in triggering the immune process leading to B-cell destruction and the development of T1DM. In addition, maternal habits (tea drinking during pregnancy), maternal diseases (pre-eclampsia, gestational diabetes and infectious diseases during pregnancy) show a significant association with T1DM in their offspring.

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