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Children with Type 1 Diabetes

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Background: The prevalence of diabetes in the Middle East is amongst the highest worldwide; Bahrain ranks amongst the top 10 countries. In particular, increasing number of children are being diagnosed with type 1 diabetes mellitus (T1DM) posing a significant public health concern.

Objective: To evaluate the magnitude of type 1 diabetes in Bahrain.

Design: A Case-Control Retrospective Study.

Setting: Pediatric Diabetes and Endocrine Clinic and Local Health Centers (LHC).

Method: Fifty-nine cases and 53 controls were included in the study. Data from the Diabetes Registry were recorded for subjects meeting the inclusion criteria and questionnaire was administered to healthy controls. Chi Square or Student's t-test was used as appropriate. Logistic regression analysis was used to evaluate independent predictors of T1DM.

Result: Fifty-nine children aged 6-12 years diagnosed with T1DM in the years 2009 and 2010 were compared to 53 healthy controls. Children with T1DM were more likely to have suffered from a pre-diabetes illness such as tonsillitis 32 (54.2%) compared to controls 3 (5.7%), and have undergone a surgery prior to diagnosis 14 (23.7%), and to have mothers with T2DM or family history of GDM. No significant difference in infant-feeding practices was observed between children with type 1 diabetes and the healthy controls.

Conclusion: Children with T1DM were more likely to have suffered from other infectious illnesses before the diagnosis was established. Whilst unable to fully investigate any potential genetic differences between cases and controls, this study provides support for the theoretical role of infections as a trigger for T1DM.

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The prevalence of diabetes in the Middle East and the North African region is considered among one of the highest worldwide[1]. Bahrain ranks amongst the top 10 countries for prevalence of diabetes; and therefore faces economic and health-care burden imposed by this disease. The World Health Organization (WHO) estimates that approximately one in four adult deaths is attributed to diabetes in the Eastern Mediterranean region, with diabetes-related deaths in Bahrain increasing from 9% in 2002 to 12% in 2010[2,3].

The increasing number of children diagnosed with type 1 diabetes mellitus (T1DM) in Bahrain is alarming; it has more than doubled in the past ten years[4]. In Bahrain, little or no data is currently available on the lifestyle, dietary, or the role of infection or childhood illnesses on the risk of T1DM. Most studies have focused only on the lifestyle and dietary intake of healthy Bahraini children[6-8].

Although no national registry exists for children with diabetes, an internal registry exists at the Pediatric Endocrine and Diabetes Unit in the Salmaniya Medical Complex (SMC).

The aim of this study is to evaluate the magnitude and risk factors of type 1 diabetes in Bahrain.

METHOD

The study subjects were children aged 6 to 12 years diagnosed with T1DM from 2009 to 2010 in the Salmaniya Medical Complex, Bahrain. The inclusion criteria were as follows:

- Registered as a confirmed case of T1DM at the Pediatric Diabetes Unit (PEU).
- 6-12 years of age at diagnosis.
- Followed up at least once at the Pediatric Diabetes Unit.
- Had a completed Diabetes Registry Form (DRF).

DRF includes personal characteristics, psychosocial, and health-related information.

Control subjects were recruited from local Health Centers across the country. Fifty-three children were selected to match the cases for age, sex and geographic location and were randomly selected. The majority of the control group selected had either the common cold or was accompanying their parents to appointments.

All data analyzed using SPSS version 21; all information was kept strictly confidential. Differences between subgroups were analyzed using Chi Square or Student's t-test as appropriate. Logistic regression analysis was used to evaluate independent predictors of T1DM. P value <0.05 was considered significant.

RESULT

Fifty-nine children met the criteria and were included in the study, compared to 53 healthy controls, see table 1. The mean age of the control group was 9.02±1.88 years and the mean age of the case group was 9.66±1.72 years. The mean BMI for the control was 48.80±35.76 and case group was 43.73±37.31. Children with T1DM were more likely to be Bahraini nationals ($p<0.001$) although there was no significant difference in self-reported race, with 95% of children being described as of Arab origin, see table 1. A significant association was identified between economic status and diabetes diagnosis ($p=0.028$) as shown in table 2.

Table 1: Baseline Characteristic of Case-Control Study

		Control 53		Cases 59		P Value
		Number and Percentage	Mean (SD[1])	Number and Percentage	Mean (SD[1])	
Age in years		53	9.02 (1.88)	59	9.66 (1.72)	0.063[a]
BMI percentile*[1]		53	48.80 (35.76)	51	43.73 (37.31)	0.505[a]
Nationality	Bahraini	50 (94.3%)		37 (62.7%)		<0.001[b]
	Non-Bahraini	3 (5.7%)		22 (37.3%)		
Gender	Male	24 (45.3%)		29 (49.2%)		0.682[b]
	Female	29 (54.7%)		30 (50.8%)		
Race	Arab	53 (100%)		56 (94.9%)		0.245[c]
	Non-Arab	0 (0.0%)		3 (5.1%)		
Religion	Muslim	53 (100%)		56 (94.9%)		0.245[c]
	Non-Muslim	0 (0.0%)		3 (5.1%)		
Governorate*[2]	Muharraq	13 (24.5%)		7 (12.1%)		0.088[b]
	Capital	7 (13.2%)		13 (22.4%)		
	Northern	18 (34%)		12 (20.7%)		
	Central	15 (28.3%)		25 (43.1%)		
	Southern	0 (0.0%)		1 (1.7%)		

[1]SD: Standard Deviation, [a]Mann Whitney,[b] Chi Squared, [c] Fisher Exact
*1 missing eight, *2 missing one

Table 2: Economic Status of Children with T1DM and Healthy Controls

		Control 53	Cases 54*	Chi-Square P-value	OR (95% CI)	Logistic Regression P-value
Economic Situation	Low	13 (24.5%)	7 (13%)	0.028	0.375 (0.175-0.802)	0.011
	Medium	34 (64.2%)	46 (85.2%)			
	High	6 (11.3%)	1 (1.9%)			

*Missing five

Medical history revealed that children with T1DM were more likely to have suffered from an illness such as tonsillitis than healthy children, 32 (54.2%) and 3 (5.7%) respectively; p<0.001 or to have undergone surgery prior to diagnosis, 14 (23.7%) and 2 (3.8%) respectively; p=0.001, see table 3. Furthermore, logistic regression analysis revealed that children who were suffering from an illness were approximately fifteen times more likely to develop diabetes [(OR 15.647) 95% CI, 4.075-60.07; P<0.001] than other children. Logistic regression showed no significant relationship (p=0.096) between surgery performed and the risk of developing diabetes. Other common diseases such as glucose-6-phosphate deficiency (G6PD), sickle cell disease/trait (SCD/SCT) and thalassemia were not found to be significantly associated with diabetes diagnosis.

Table 3: Medical History of Children with T1DM and Healthy Controls

		Controls 53	Cases 59	P-value	OR (95% CI)	Logistic Regression P-value
G6PD[1]	No	51 (96.2%)	53 (89.8%)	0.277[b]	8.656 (0.342-218.56)	0.190
	Yes	2 (3.8%)	6 (10.2%)			
SCD/SCT[2]	No	45 (84.9%)	55 (93.2%)	0.155[a]	0.454 (0.099-2.308)	0.341
	Yes	8 (15.1%)	4 (6.8%)			
Thalassemia/ Trait	No	51 (96.2%)	58 (98.3%)	0.602[b]	0.058 (0.002-1.894)	0.109
	Yes	2 (3.8%)	1 (1.7%)			
Surgeries	No	51 (96.2%)	45 (76.3%)	**0.003[a]**	4.687 (0.761-28.86)	0.096
	Yes	2 (3.8%)	14 (23.7%)			
Child Illness	No	50 (94.3%)	27 (45.8%)	**< 0.001[b]**	**15.647 (4.075-60.074)**	**< 0.001**
	Yes	3 (5.7%)	32 (54.2%)			

[a]Chi Squared, [b]Fisher Exact [1]G6PD: Glucose-6-Phosphate deficiency [2]SCD/SCT Sickle-cell disease/Sickle-cell trait

Mothers of T1DM children are more likely to have had gestational diabetes (GDM) (P=0.053) and to have used medication during pregnancy than mothers with healthy children, see table 3. Logistic regression analysis showed a significant but weak association [OR 1.7, 95% CI (1.086-2.637)] between maternal use of medication and the risk of offspring's developing diabetes; also no significant relationship was found for mothers with GDM (P=0.065). Pregnancy complications, gestational hypertension or prescribed drug use and exposure to toxins were not found to be significantly associated with diabetes diagnosis, see table 4. Family history of T1DM was rarely reported in either group. No significant and independent relationship between parental hypertension and diabetes, see table 5.

Table 4: Pre and Postnatal Maternal History

		Control 53	Cases 59	P-Value	OR (95% CI)	Logistic Regression P-Value
Pregnancy Complications	Yes	7 (13.2%)	11 (18.6%)	0.434a	0.984 (0.276-3.504)	0.981
Gestational DM	Yes	4 (7.5%)	12 (20.3%)	**0.053a**	3.220 (0.932-11.127)	0.065
Gestational HTN	Yes	3 (5.7%)	9 (15.3%)	0.095a	3.685 (0.774-17.53)	0.101
Medication use during pregnancy	Yes	12 (22.6%)	8 (13.6%)	**0.034a**	1.704 (1.086-2.637)	**0.020**
Smoking/Drug use during pregnancy	Yes	1 (1.9%)	2 (3.4%)	1.000b	0.868 (0.05-13.947)	0.921
Toxin/ Radiation Exposure in pregnancy	Yes	1 (1.9%)	3 (5.1%)	0.620b	2.400 (0.213-27.081)	0.479

[a]Chi Squared, [b]Fisher Exact

Table 5: Parental History of Diabetes and Hypertension

		Control 53	Cases 59	P-Value	Logistic Regression P-Value
Maternal Hx T1DM	No	53 (100.0%)	59 (100.0%)	-	-
	Yes	0 (0.0%)	0 (0.0%)		
Paternal Hx T1DM	No	52 (98.1%)	58 (98.3%)	1.000[b]	0.999
	Yes	1 (1.9%)	1 (1.7%)		
Maternal Hx* T2DM	No	53 (100.0%)	53 (91.4%)	**0.058[b]**	0.999
	Yes	0 (0.0%)	5 (8.6%)		
Paternal Hx T2DM	No	47 (88.7%)	51 (86.4%)	0.781[a]	0.619
	Yes	6 (11.3%)	8 (13.6%)		
Mother Hx Hypertension	No	53 (100.0%)	54 (91.5%)	**0.059[a]**	0.999
	Yes	0 (0.0%)	5 (8.5%)		
Paternal Hx Hypertension	No	53 (100.0%)	57 (96.6%)	0.497[b]	0.999
	Yes	0 (0.0%)	2 (3.4%)		

[a]Mann Whitney, [b]Chi Squared. *missing one

No significant difference between children with T1DM and their healthy controls was found for infant-feeding practices, see table 6.

Table 6: Infant Feeding History of Children with T1DM and Healthy Controls

			Control 53	Cases 58*	Chi-Square P-value	OR (95% CI)	Logistic Regression P-value
Feeding History	**Bottle Fed**		4 (7.5%)	3 (5.2%)	0.769	0.918 (0.755-1.115)	0.389
	Mixed feeding (breast & bottle)		4 (7.5%)	9 (15.5%)			
	EBF <6 months		9 (17.0%)	12 (20.7%)			
	Breastfed	6≤12 months	5 (9.5%)	5 (8.6%)			
		12≤18 months	9 (17.0%)	10 (17.2%)			
		≥18 months	22 (41.5%)	19 (32.8%)			

*Missing data

DISCUSSION

The exact mechanism remains unknown; there is a general consensus that both genetics and the environment play a role[9-11]. Despite the strong evidence of genetics in the development of T1DM, the steady and rapid rise of the disease does not appear to be solely attributed to changes in the gene pool[12]. A possible explanation is environmental triggers that instigate a cascade of events leading to the development of T1DM either by direct or indirect means or by interacting with existing susceptible genes.

This study supports the role of infection as a potential trigger for T1DM because over half of the children with T1DM have suffered from an illness prior to diagnosis[5]. Seasonal variation in diabetes diagnoses revealed higher incidence in the winter months which supports the premise that viral infections either trigger or accelerate the destruction of beta cells[12,13]. Although children with diabetes were more likely to have undergone a surgery, no details were given as to the type of surgery performed. Cardwell et al found no increased risk of T1DM in children who had tonsillectomy or adenoidectomy[14].

The fact that mothers of children with T1DM were more likely to have T2DM, GDM, or a family history of GDM points to a possible relationship between the intrauterine environment and diabetes occurrence. Penderson was the first to describe the association between infant birth weight, length and maternal diabetes; several subsequent studies have further examined the metabolic effects in-utero[15-17]. It appears that even minor changes in the equilibrium of the intrauterine environment may have long-term effects beyond simply the perinatal period[18]. Congenital rubella is the only known virus that directly causes T1DM in the offspring, but recent studies have also implicated maternal enteroviral infection such as Coxsackie B virus in the etiology of T1DM[19-21].

Studies have also looked into the association between breastfeeding and T1DM[20-24]. Although over 90% of the children in the current study had received breast milk at one point, the importance of infant-feeding practice could not be confirmed. Some studies have found a protective effect of breastfeeding via protection against enteroviruses or by means of delayed introduction of cow's milk protein, other studies found no significant relationship between breastfeeding and diabetes occurrence[24-27]. Some studies have hypothesized that low levels of vitamin D in breast milk are a potential risk factor for diabetes development and that supplementation with vitamin D may be required to confer a protective effect[28].

This study was limited for being retrospective and not able to further investigate the role of genetics or environmental triggers in the development of diabetes or the role of breast feeding due to the high prevalence of breastfeeding in both groups.

CONCLUSION

Children with T1DM were more likely to have suffered from other infectious illnesses before the diagnosis was established.

This study highlights the need for further research to investigate the potential inter-generational transfer or risk via maternal impaired glucose tolerance.

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