Prevalence and special clinical and biochemical characteristics of familial type 1 (insulin dependent) diabetes mellitus in pediatric patients in a tertiary care setting

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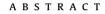[b] College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia
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A R T I C L E   I N F O

A B S T R A C T

Background and Objectives: The hereditable nature of type 1 diabetes mellitus (T1DM) makes it a condition that is in some cases shared among siblings. Studies that focus on the epidemiology of T1DM among siblings are scarce. The primary focus of the study is to estimate the prevalence of familial T1DM among siblings and the secondary focus is to identify the presence of any special clinical or biochemical characteristics specific to this entity.
Methods: In a retrospective cross-sectional study, the charts of 308 children (>1 year) diagnosed with type 1 diabetes mellitus in a Saudi tertiary care setting were reviewed. The patients who have one sibling or more with T1DM were included. The prevalence of familial T1DM among siblings was calculated, and specific clinical and biochemical characteristics were investigated. Data were analyzed using Statistical Package for the Social Sciences software version 22 (IBM SPSS Statistics for Windows). The control group includes all patients with type I DM who were excluded for sibling with DM.
Results: The prevalence of familial T1DM among siblings was estimated at 15.9%. Seventy-four percent of the patients with a positive family history of diabetes mellitus had one affected sibling only. The clinical presentation showed no significant differences relative to the age of presentation, gender, parental consanguinity, diabetic ketoacidosis at presentation, and its number of episodes. For the biochemical characteristics, autoantibody tests revealed no statistically significant difference, but the mean initial HbA1c levels were lower in patients who had diabetic siblings.
Conclusion: The prevalence of familial T1DM was found to be higher than that reported in other studies. No specific clinical or biochemical features were found to characterize familial T1DM among siblings.

What is already known on this topic?

Many patients with T1DM have siblings who also suffer from the disease. The prevalence and clinical and biochemical characteristics of this specific population have not been well defined in the literature.

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized in 95% of cases by the destruction of the insulin-secreting cells of the pancreas by T lymphocytes. Islet Cell Autoantibodies (ICA), Insulin Autoantibodies (IAA), and Glutamic Acid Decarboxylase antibodies (GAD) are the markers for the autoimmunity [1–3]. The patient experiences symptoms of polydipsia,

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polyuria, weight loss, fatigue, and blurred vision [1,2], and 5% of cases are idiopathic. Long-term complications include acute complications such as diabetic ketoacidosis (DKA) and chronic complications such as nephropathies, retinopathies, and neuropathies [1,2]. The burden of diabetes is generally immense, reducing life expectancy by almost a third [1], affecting quality of life, and being a major source of direct and indirect expenditures [4]. The risk of developing T1DM increases sharply until the age of 14 and declines thereafter [2], but in some cases, it appears later in adulthood [1]. It accounts for 5–10% of all the diabetes cases worldwide [5]. Data on the prevalence of T1DM in children are mostly available from high-income countries [6]. Currently there are more than 1,105,500 children (0–14 years) affected by T1DM [6]. As for incidence, it increased by 2.3% per year over the past 3 decades (95% CI 1.6–3.1) [7] and is reported to be 86,000 cases in 2015 [6]. Incidence of T1DM varies dramatically between countries. For example, annual incidence in Finland was 36.5/100,000, in Kuwait was 18.3/100,000, in Sudan was 5/100,000, and in China was 0.1/100,000 [8]. This global variation reflects the involvement of multiple genetic and environmental factors in the etiology of the disease, which makes it multifactorial [9–11].

In Saudi Arabia, a national study revealed a prevalence rate of 190.5 per 100,000, mostly in the central and southern regions [12]. Saudi Arabia also has the third highest rate of T1DM diagnosis in children aged 0–14 years, with an incidence of 31.4 per 100,000 [13], and one of the highest frequencies of DKA [14]. Furthermore, consanguineous marriages are highly prevalent in Saudi society, accounting for more than 50% of all marriages, which contributes to a high incidence of genetic diseases [15–18].

Genetic and environmental risk factors have been associated with an increased risk of T1DM [19,20]. Infections, dietary factors [21,22], and geographical area are also other risk factors. Twin studies showed that T1DM clusters in families [23–25]. Monozygotic twins have 30–50% chance of developing T1DM compared to dizygotic twins (15%), indicating that a shared environment accounts for little effect than genetic effect [23,24]. The major T1D susceptibility locus maps to the HLA class II genes at 6p21 and accounts for up to 30%–50% of genetic T1D risk, and in siblings, the risk of developing T1DM ranges from 3 to 20% depending on the HLA matching [1]. Moreover, an association was observed with the prevalence of evolving diabetes in first-degree relatives [26,27]. Other non-HLA T1D loci in combination have smaller effects on disease risk as compared to HLA [40].

Data related to the prevalence and characteristics of T1DM among siblings are scarce. Hence, this study estimated the prevalence and the specific clinical characteristics such as age at diagnosis, DKA episodes, and biochemical features including HbA1C levels and autoantibody tests status (positive or negative) of familial T1DM among siblings. Investigating these characteristics might help to predict the likelihood of diagnosing T1DM among siblings.

2. Methods

This retrospective cross-sectional study was approved by King Abdullah International Medical Research Center (KAIMRC), SP14/ 122. It included all pediatric patients (1–14 years) diagnosed with T1DM at the pediatric endocrinology department in King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia, over a 10-year-period between January 2003 to December 2013. Patients who did not have siblings or who were diagnosed with any other type of diabetes were excluded and used as a control group. The diagnosis of T1DM was made based on the WHO criteria [1].

Data were collected from the patients' medical records, and demographic variables (gender, parental consanguinity, and sage at

diagnosis) and axiological data (weight, height, and body mass index (BMI)) were extracted. BMI was categorized into 3 levels (above 95th percentile, normal, and below the 5th percentile) following the Centers for Disease Control and Prevention (CDC) growth chart for BMI. Prevalence of familial T1DM among siblings was calculated based on the presence or absence of any diabetic sibling. Other variables included the number of diabetic siblings, clinical factors such as initial DKA presentation, and total number of DKA episodes since diagnosis. According to the British Society for Pediatric Endocrinology and Diabetes (BSPED), DKA is defined as acidosis (indicated by blood pH below 7.3 or plasma bicarbonate below 18 mmol/liter) and ketonemia (indicated by blood beta-hydroxybutyrate above 3 mmol/L). Biochemical characteristics such as autoantibody test (ICA, IAA, and GAD) results, which were systematically reviewed and defined as positive or negative according to the reference range reported by the laboratory and initial HbA1c level (as a percent) (glycated hemoglobin), were also investigated; not all autoantibody tests were performed in each patient. Any sort of patient identification was not utilized; unique identifiers (serial numbers) were used to insure patients' confidentiality.

Patients were classified into two groups: familial group (with one or more affected siblings) and non-familial group (with no affected siblings). The clinical and biochemical presenting features were examined and compared between these two groups.

2.1. Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences software version 22 (IBM SPSS Statistics for Windows). Categorical variables are presented as frequencies (percentages). Numerical variables are described as mean and standard deviations (SD) and were tested for normality using Kolmogorov-Smirnov and Shapiro-Walk tests. Chi-squared test was used to compare between the outcome variable groups and all categorical variables. For non-parametric data, the Mann-Whitney U and Kruskal-Wallis tests were used to compare the two groups. The prevalence is described as a percentage. Levels of significance were set at $P < .05$.

3. Results

Three-hundred and eight patients with T1DM who had siblings were included in the study. Demographic characteristics of the study subjects are presented in Table 1. Of these, almost half (51%) were females. Regarding parental consanguinity, 30.9% of the parents were third-degree cousins. Mean age-at-diagnosis was 7.8 years ± 3.9, with peak age of diagnosis at 12 years (33 patients) and 8 years (30 patients). The peak months of presentation were September and December with 40 and 44 cases, respectively, followed by 35 cases in October. More than half of the patients (55.6%) had normal BMI at the time of diagnosis, as shown in Table 1.

With regard to the clinical and biochemical characteristics, 136 patients (44.2%) presented initially with DKA. The mean level of initial glycated hemoglobin (HbA1c) was 11.1 ± 2.6. More than half of the subjects (57.8%) had a positive GAD autoantibody test, followed by positive IAA (28.1%) and ICA (24.6%) tests. Among the patients who underwent the autoantibody tests, GAD antibodies had the highest positive percentage (73.6%), followed by IAA (48%) and ICA (28.9%).

Forty-nine patients had at least one sibling also diagnosed with T1DM, which allowed for an estimated prevalence of 15.9% of familial T1DM among siblings. Of those with a positive family history among siblings, the majority (79.6%) had one affected sibling.

Table 2 shows the bivariate analysis of the outcome variable (diabetic sibling vs. non-diabetic siblings) with all independent

Table 1
General, clinical, and biochemical characteristics of T1DM patients (n = 308).

Variable	Frequency (%)
Gender	
Male	151 (49.0)
Female	157 (51.0)
Age at diagnosis (Mean ± SD, years)	7.8 ± 3.9
Parental consanguinity	
No	195 (69.1)
Yes	87 (30.9)
BMI[a]	
Overweight	46 (18.2)
Normal	140 (55.6)
Underweight	66 (26.2)
Having a diabetic sibling	49 (15.9)
Number of diabetic siblings(N = 49)	
1	39 (79.6)
2	8 (16.3)
3	2 (4.1)
Initial DKA[b] **presentation**	
No	172 (55.8)
Yes	136 (44.2)
Total number of DKA episodes (Mean ± SD)	1.3 ± 2.4
Initial HbA1C[c] (mean ± SD, %)	11.1 ± 2.6
GAD[d]	
Positive	159 (57.8),73.6%[g]
Negative	57 (20.7)
Not done	59 (21.5)
ICA[e]	
Positive	71 (24.6), 28.9%[g]
Negative	174 (60.2)
Not done	44 (15.2)
IAA[f]	
Positive	76 (28.1),48%[g]
Negative	83 (30.7)
Not done	111 (41.1)

  [a] BMI: body mass index.
  [b] DKA: diabetic ketoacidosis.
  [c] HbA1C: hemoglobin A1C.
  [d] GAD: glutamic acid decarboxylase.
  [e] ICA: islet cell autoantibody.
  [f] IAA: insulin autoantibody.
  [g] percentage among those who had the test.

variables. Gender, BMI, and initial DKA presentation were not significantly associated with having a diabetic sibling. Parental consanguinity showed marginal significance and is more frequent in the diabetic sibling. Autoantibody tests also showed no significant difference between both groups except in those who had more than one negative antibody which was statistically significant in the familial group ($P = .02$). The nonparametric tests done for the non-normal continuous variables revealed no association between age of presentation and number of DKA episodes with the diabetic sibling group; however, the mean initial HbA1C was significantly lower in the diabetic sibling group.

4. Discussion

This study aimed to determine the prevalence and the clinical and biochemical characteristics of familial T1DM among siblings. The prevalence of familial T1DM was estimated at 15.9%, which is higher than that reported by other studies [28–30]. Genetic risk for T1DM has been demonstrated in several studies, whereby family history significantly increased the likelihood of getting diagnosed [9–11], of which almost a quarter was accounted for by siblings [30–34]. Although parents' consanguinity has OR of 3.72 in patients with a diabetic sibling compared to those with a non-diabetic sibling, the P value was not significant, $P = .05$. However, with this trend toward significance, a larger sample size of patients with diabetic sibling can affirm the significance of consanguinity in

patients with T1DM.

With regard to sex, males and females had a similar distribution, which is consistent with the literature [22,28]. The mean age of presentation was 7.8 years ± 3.9 compared to another study where the mean age was from 5.9 to 7 years old [19]. The peak age of diagnosis was 12 years, which is concordant with the highest age specific incidence of T1DM in the age group of 10–14 [10]. More than 40% of subjects presented initially with DKA, which is double that reported by a European study [31]. The initial DKA presentation is lower than that reported 25 years ago in Saudi Arabia [30], and its recurrence is similar to that reported in another study [32]. GAD autoantibody was the most prevalent autoantibody, which is also reported elsewhere [3,33].

In our study, no unique clinical or biochemical features of T1DM among siblings were observed compared to studies documenting female predominance, mean age 9.7 ± 4.9 years, and lower levels of DKA in patients with diabetic siblings [34]. However, HbA1c levels were significantly lower in patients with diabetic siblings, which should be due to prior recognition of the disease. Some studies reported no difference in antibodies between familial and non-familial diabetes [35], and others reported higher insulin autoantibody [36].

The diagnosis of type 1 diabetes should be re-evaluated in Persistently Autoantibody Negative (PAN) patients because a subset has monogenic or Type 2 diabetes. The remaining PAN have relatively preserved C-peptide compared with autoantibody positive (ab+), suggesting slower β-cell destruction, but a very high frequency of diabetogenic HLA implying that type 1B (idiopathic) diabetes is rare [37].

In another study using next-generation sequencing, they screened the HNF1A, HNF4A, HNF1B, GCK, and INS genes in all 469 children (12.1%) who tested negative for both GAD and IA-2 autoantibodies and in 469 antibody-positive matched controls selected from the Norwegian Childhood Diabetes Registry (3,882 children). Their results suggested that the prevalence of MODY in antibody-negative childhood diabetes may reach 6.5%, and clinicians had not recognized one-third of these MODY cases from their clinical data [38].

In one of our local studies, we showed a strong association of HLADQB1*0201/0302 and DRB1*03/04 with T1DM. Thus, combining genetic markers with autoantibodies is useful in a screening program for early detection of T1DM among Saudi children, specially for siblings who are at higher risk [39].

One limitation of this study is that it was in a single center, and thus the number of subjects was limited. The autoantibodies tests (GAD, ICA, and IAA) were not performed in all patients; this might have led to an underestimation of the true association of this test with the outcome, possible confounding factor of coexistence parents with T1DM which could be the main reason of T1DM inheritance in both index case and their siblings. Although it was a retrospective study, most of the data were digitalized objective variables that were easy and accurately extracted, and thus the risk of bias is decreased.

In conclusion, it was found that King Abdulaziz Medical City has higher prevalence of siblings with type 1 diabetes, but there was no major difference between diabetic patients with diabetic siblings vs. diabetic patients with no diabetic sibling in terms of clinical and biochemical characteristics.

We recommend conducting more studies in this field to explain the increased prevalence of siblings with T1DM.

Authorship contributions

AM and NS drafted this manuscript. Clinical data, analyzed data, and performed experiments. AM, Am, and NS designed this study.

Table 2
Frequency distributions and bivariate associations of the study variables among diabetic siblings and non-diabetic siblings.

Variable	Diabetic siblings (N = 49) n (%)	Non-diabetic siblings (N = 259) n (%)	Total (N = 308) n (%)	P value
Gender				
Male	27 (55.1)	124 (47.9)	151 (49)	.42
Female	22 (44.9)	135(52.1)	157 (51)	
Mean age (Mean, SD)	8 (4.1)	7.7 (3.9)	−	.66
Parental consanguinity				
Yes	19 (43.2)	68(28.6)	87 (30.9)	.05
No	25 (56.8)	170 (71.4)	195 (69.1)	
Initial DKA presentation				
Yes	23 (53.1)	113(43.6)	136 (44.2)	.67
No	26 (46.9)	146 (56.4)	172 (55.8)	
BMI[a]				
Overweight	6 (15.0)	40 (18.9)	46 (18.3)	.10
Normal	18 (45.0)	122 (57.5)	140 (55.6)	
Underweight	16 (40.0)	50 (23.6)	66 (26.2)	
Number of DKA[b] episodes (Mean, SD)	1.4 (2.4)	1.3 (2.4)	−	.51
Mean initial HbA1C[c]	10.5 (2.4)	11.3 (2.6)	−	.03[g]
GAD [d]autoantibody test				
Positive	30 (68.2)	129 (55.8)	159 (57.8)	.11
Negative	4 (9.1)	53 (22.9)	57 (20.7)	
Not done	10 (22.7)	49 (21.2)	59 (21.5)	
ICA[e] test				
Positive	10 (22.2)	61 (25.0)	71 (24.6)	.62
Negative	26 (57.8)	148 (60.7)	174 (60.2)	
Not done	9 (20.0)	35 (14.3)	44 (15.2)	
IAA[f] test				
Positive	17 (38.6)	59 (26.1)	76 (28.1)	.09
Negative	8 (18.2)	75 (33.2)	83 (30.7)	
Not done	19 (43.2)	92 (40.7)	111 (41.1)	
>1 negative antibody				
No	30 (83.3)	121 (62.4)	151 (65.7)	.02[g]
Yes	6 (16.7)	73 (37.6)	79 (34.3)	

[a] BMI: body mass index.
[b] DKA: diabetic ketoacidosis.
[c] HbA1C: hemoglobin A1C.
[d] GAD: glutamic acid decarboxylase.
[e] ICA: islet cell autoantibody.
[f] IAA: insulin autoantibody.
[g] Statistically significant.

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