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Retrospective comparative analysis of metabolic control and early complications in familial and sporadic type 1 diabetes patients☆

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ABSTRACT

Background: Genetic susceptibility and lifestyle are associated with glycemic control and diabetic complications in type 1 diabetes (T1D).

Objectives: To investigate metabolic control and occurrence of acute and microvascular complications among familial and sporadic T1D patients.

Patients and Methods: Retrieved from our institutional registry of new T1D cases for the years 1979–2008 were 226 familial patients belonging to 121 families (58 parent–offspring, 63 sib-pairs) and 226 sporadic cases matched for age, gender, and year of diagnosis. Extracted from medical files were clinical course and therapeutic regimen.

Results: Mean age at diagnosis of diabetes of the cohort was 10.8 ± 5.7 years. Throughout follow-up (11.1 ± 8.7 years) mean HbA1c values were significantly higher in familial than in sporadic cases (8.18% ± 1.15% vs. 7.85% ± 1.15%, p = 0.005). Diabetic ketoacidosis (DKA) rates were higher in familial than sporadic cases (2.8 vs. 1.9 events per 100 patient-years; incidence rate ratio (IRR) = 1.5, 95% CI [1.03, 2.22, p = 0.03]). Severe hypoglycemia events per 100 patient-years were comparable in familial and sporadic groups (3.7 vs. 4.0 events); sib-pairs had higher rates than parent–offspring (4.8 vs. 2.4 events; (IRR) = 2, 95% CI [1.03, 3.25, p = 0.03]). The percentage of patients with microvascular complications was similar in the familial (21.7%) and sporadic (26.7%) groups. In both familial and sporadic cases the most significant predictor for metabolic control and microvascular complications was diabetes duration; a higher mean HbA1c level was the predictor for DKA events.

Conclusions: The worse metabolic control and increased rate of DKA in familial T1D patients as compared to those in the sporadic T1D patients warrant intensified surveillance in this population.

1. Introduction

Type 1 diabetes mellitus (T1D) is associated with considerable morbidity from a variety of short- and long-term complications. Short-term complications, i.e. diabetic ketoacidosis (DKA) and severe hypoglycemia, are acute and sometimes life-threatening conditions generally resulting from inadequate metabolic control, and may develop at any time after diagnosis of T1D (Bulsara, Davis, Holman, & Jones, 2004; Levine, Anderson, Butler, Antisdel, Brackett, & Laffel, 2001; Rewers et al., 2002; Urbach, LaFranchi, Lambert, Lapidus, Daneman, & Becker, 2005). Long-term complications, i.e. microvascular damage manifested as retinopathy, nephropathy, or neuropathy, are caused by longstanding increased or fluctuating blood glucose levels. Although during the pediatric and adolescent years these complications are usually sub-clinical, over time they may lead to impaired vision, renal failure, and severe neuropathic pain (DCCT Research Group, 1994; Diabetes Control and Complications Trial Research Group 1993; Reichard, Nilsson, & Rosenqvist, 1993).

The importance of metabolic control in reducing and delaying complications (Diabetes Control and Complications Trial Research Group, 1993; Reichard et al., 1993) and the contribution of early detection and treatment of microvascular complications (Diabetes Control and Complications Trial Research Group, 1994) have been well established. The routine care of our T1D patients therefore includes a quarterly hemoglobin A1c (HbA1c) determination and annual screening for microvascular diabetes complications (American Diabetes Association, 2011).

It has previously been demonstrated that age at onset of diabetes, chronological age and pubertal stage, duration of diabetes, and glycemic control are critical factors contributing toward the development of microvascular complications (Donaghue et al., 2003;

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Svensson, Eriksson, & Dahlquist, 2004). In addition, clustering of diabetic nephropathy and retinopathy in families and in specific ethnic groups points towards a genetic predisposition as well (Borch-Johnsen et al., 1992; Bowden 2002; Diabetes Control and Complications Trial Research Group, 1997; Hietala, Forsblom, Summanen, Groop, & Finn Diane Study Group, 2008; Quinn, Angelico, Warram, & Krolewski, 1996; Seaquist, Goetz, Rich, & Barbosa, 1989). On the basis of this assumption we addressed the question as to whether the development and evolution of diabetic complications differ in familial and sporadic T1D patients.

In the past 30 years 226 patients with familial T1D were followed in our tertiary center; these patients were categorized into parent–offspring (98 patients) and sib-pair (128 patients) subgroups. Recently we published a retrospective–comparative analysis of the demographic and clinical characteristics at presentation of familial and sporadic T1D cases demonstrating a significant distinction in gender distribution and age at onset of diabetes between the two subgroups: male preponderance and younger age of the offspring distinguished the parent–offspring from the sib-pairs group (Lebenthal, de Vries, Phillip, & Lazar, 2010). In the present retrospective study we extended our research to determine the metabolic control and occurrence of diabetic complications in this cohort. Our objectives were to compare the metabolic control stratified by age in familial and sporadic T1D patients as well as the prevalence, type, and timing of appearance of acute and microvascular complications in the two groups and in the familial subgroups.

2. Patients and Methods

2.1. Patients

Our institutional diabetes registry is consecutive and includes demographic data (date of diagnosis, date of birth, and gender) of every new-onset diabetic patient referred to our clinic. Survey of this registry for all cases of familial T1D diagnosed and followed between 1979 and 2008 yielded 226 patients belonging to 121 multiplex families: 58 parent–offspring families and 63 sib-pair families. All families met the following inclusion criteria: T1D in two or more first-degree relatives; T1D diagnosed after the age of 6 months. Excluded from the study were patients with other types of diabetes as previously reported (Lebenthal et al., 2010). The control population comprising 226 sporadic T1D patients was also extracted from the institutional registry. For each familial case, we randomly assigned the next consecutively-diagnosed patient with sporadic T1D who matched the familial cases by age, gender, and year of diagnosis, and remained sporadic till December 2008. All patients were followed in our tertiary care center and were transferred to Adult Diabetes Clinics at the age of 35–40 years.

Extracted from their medical files were demographic data, date of diagnosis of T1D, HbA1c levels, episodes of DKA and severe hypoglycemia, insulin regimen, whether 3–4 multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), and presence of retinopathy, nephropathy, or neuropathy. The demographic data are presented in Table 1. The longitudinal data regarding mode of therapy, HbA1c levels, and acute and microvascular complications throughout follow-up, were stratified according to patient's age group (<6, 6–12, 12–19, >19 years). Stratification into these groups was selected in order to match the age groups recommended by the American Diabetes Association (ADA) for HbA1c treatment goals (≤8.5% for patients aged <6 years, ≤8% for 6–12 years, <7.5% for 12–19 years, <7.0% for >19 years) (American Diabetes Association, 2011). Although in the latest ISPAD guidelines the recommended HbA1c target range for all ages is less than 7.5% (Rewers, Pihoker, Donaghue, Hanas, Swift, & Klingensmith, 2007), we have used the ADA-recommended HbA1c target goals, which change for the different ages, since these were used for our patients until 2008.

The Familial T1D study protocol was approved by our Institutional Review Board.

2.2. Methods

HbA1c was routinely tested at 3-month intervals. Overall mean HbA1c was calculated as the mean of all available HbA1c values of each patient throughout the follow-up period. Interim mean HbA1c was calculated as the mean of all available HbA1c values of each patient in each age group. Longitudinal data analyses of HbA1c was inappropriate since age of diagnosis of the studied cohort was heterogeneous (range: 0.8–34.5 years; 95% CI: 10.2–11.3 years), therefore each age interval was analyzed separately.

Between the years 1978 and 1994 HbA1 levels were measured by ion-exchange chromatography (Glyc-Affin GHb, Isolab Inc., Akron, Ohio, USA); after 1994 capillary HbA1c values were determined using an automated immunochemical technique (DCA 2000; Siemens Medical Solutions Diagnostics, Tarrytown, NY); the 95% confidence limits (mean ± 2 SD) are 4.3% to 5.7%. The conversion equation from HbA1 to HbA1c is HbA1c = 2.409 + 0.617*(HbA1).

DKA events were defined as blood pH <7.3 with bicarbonate <15 mEq/l and need for intravenous fluid and insulin infusion. Severe hypoglycemic events were defined as coma and/or seizures or the

Table 1
Demographic characteristics, mode of therapy, and metabolic control of familial and sporadic T1D cases and of familial subgroups (parent–offspring and sib-pairs).

	Familial T1D	Sporadic T1D	P	Familial T1D Parent–offspring	Familial T1D Sib-pairs	P
Number	226	226		98	128	
Demographic characteristics						
Duration of F/U (years)	11.1 ± 8.7	11.4 ± 8.7	0.676	11.5 ± 9.4	10.8 ± 8.3	0.517
Age at diagnosis (years)	10.8 ± 5.9	10.8 ± 5.5	0.956	11.5 ± 6.9	10.2 ± 4.9	0.101
Male Gender (%)	119 (52.7)	119 (52.7)	1	59 (60.2)	60 (46.9)	0.047
Mode of therapy—Patients on Multiple Daily Injections (%)						
<6 years	93.3 (n = 43)	87.8 (n = 41)	0.378	94.4 (n = 18)	92.6 (n = 25)	0.807
6–12 years	82.9 (n = 116)	79.8 (n = 116)	0.547	87.7 (n = 43)	75.0 (n = 73)	0.078
12–19 years	86.3 (n = 116)	76.5 (n = 116)	0.027	79.2 (n = 53)	90 (n = 100)	0.074
>19 years	62.4 (n = 114)	54.6 (n = 123)	0.219	60.4 (n = 46)	63.8 (n = 68)	0.713
Metabolic control as expressed by mean HbA1c (%)*						
Overall mean HbA1c (%)	8.18 ± 1.15 (n = 226)	7.85 ± 1.15 (n = 226)	0.005	8.01 ± 1.12(n = 98)	8.30 ± 1.16 (n = 128)	0.121
<6 years	8.39 ± 1.23 (n = 43)	8.20 ± 1.15 (n = 41)	0.760	8.09 ± 1.18 (n = 18)	8.59 ± 1.24 (n = 25)	0.218
6–12 years	8.45 ± 1.32 (n = 116)	7.93 ± 1.18 (n = 116)	0.001	8.25 ± 1.36 (n = 43)	8.56 ± 1.29 (n = 73)	0.150
12–19 years	8.75 ± 1.46 (n = 153)	8.16 ± 1.40 (n = 148)	<0.001	8.73 ± 1.46 (n = 53)	8.76 ± 1.46 (n = 100)	0.988
>19 years	7.64 ± 1.22 (n = 114)	7.77 ± 1.31 (n = 123)	0.488	7.75 ± 1.09 (n = 46)	7.57 ± 1.30 (n = 68)	0.579

T1D = type1 diabetes mellitus; n = number; NS = non-significant; F/U = follow-up. Values expressed as mean ± SD.
* Mixed models for repeated measures were applied.