Original article

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Epidemiological features of type 1 diabetes mellitus in children and adolescents over a 5-year period - a single centre experience

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Objective – To investigate the epidemiological, clinical and laboratory features of children and adolescents with newly diagnosed type 1 diabetes mellitus (T1DM) treated at the Clinical Hospital Centre, Rijeka. **Methods** – The medical records of 83 hospitalized children were analysed retrospectively by gender and age subgroups. **Results** – The mean age of children at diagnosis was 8.40±4.82 years. At T1DM onset, the number of children ≤5, between 6-10 and ≥11 years old was 31 (37.3%), 23 (27.7%) and 29 (34.9%), respectively. The patients were mostly diagnosed at ages 2-4 years (18.1%), followed by the 12-14 years age group (15.7%). Mean duration of symptoms was 21.96±27.92 days. The symptoms lasted significantly longer (P=0.0116) and mean glycosylated hemoglobin A1c (HbA1c) was significantly higher (P=0.0039) in the ≥11 years subgroup. Polyuria and polydipsia were the most common symptoms (90.36%). 25.3% of patients had diabetic ketoacidosis (DKA). **Conclusion** – The age at T1DM onset has been decreasing. The symptoms lasted significantly longer and mean HbA1c levels were significantly higher in older children. The incidence of DKA in children with newly diagnosed T1DM is still high and includes one quarter of all patients.

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by insulin deficiency, following destruction of the insulin-producing pancreatic beta cells. The disease requires lifelong subcutaneous administration of insulin. Acute and chronic complications of diabetes are a result of the disproportion between the actual concentration of insulin given subcutaneously and the actual physiological needs at that moment. T1DM is the most common form of diabetes in children and adolescents, despite the increasing rate of type 2 diabetes (1). More than 85% of patients with diabetes under the age of 20 years suffer from T1DM (2). The epidemiology of T1DM has been changing in the last 50 years. While the incidence of the disease has been increasing by 2-5% annually, the age at diagnosis has been decreasing, especially in children under the age of 5 (3-9). This increase in T1DM incidence suggests that, in addition to genetic predisposition, environmental factors play a significant role in the aetiology of the disease. Moreover, T1DM is being diagnosed more often in patients with low genetic susceptibility (10, 11). Epidemiological studies are important for monitoring changes in the features of diabetes, and to develop strategies for early recognition, prevention and treatment of the disease.

The aim of this study was to determine epidemiological, clinical and laboratory features of children and adolescents under the age of 18 years with newly-diagnosed T1DM, treated in the Department of Paediatrics, Medical Hospital Centre Rijeka during a five-year period.

Methods

Newly-diagnosed T1DM patients between 0 and 18 years, hospitalized in the Department of Paediatrics, Endocrinology, Medical Hospital Centre Rijeka between January 1, 2011 and December 31, 2015, were included in the study. The diagnosis of T1DM was made in accordance with the criteria of the World Health Organization (12). The day of the first insulin dose was taken as the point of onset of the disease.

Diabetic ketoacidosis (DKA) was defined as blood glucose >11 mmol/l, venous pH <7.30 or bicarbonate <15 mmol/l and ketonuria. The severity of DKA was categorized according to the degree of acidosis as mild (venous pH <7.3, bicarbonate <15 mmol/l), moderate (venous pH <7.2, bicarbonate <10 mmol/l) or severe (venous pH<7.1, bicarbonate <5 mmol/l) (13). The medical records of the patients were reviewed retrospectively.

All patients with T1DM were evaluated for: date of hospitalization, age at T1DM onset, sex, symptoms, duration of symptoms, season of presentation, the history of diabetes in first-degree relatives, laboratory findings including urinary ketone content, the results of blood biochemistry including blood glucose, blood pH, glycosylated haemoglobin A1c (HbA1c) levels, anti-glutamic acid decarboxylase autoantibodies (GAD Ab), islet cell autoantibodies (ICA), tyrosine phosphatase islet autoantibodies (IA2 Ab), anti-thyroid peroxidase and anti-thyroglobulin autoantibodies and tissue transglutaminase antibodies (t-TG Ab). The collected data were analysed for the study group, by gender and age subgroups (≤5, 6-10, ≥11 years).

Statistical analysis

Statistical analysis was conducted using the Statistical Package STATA 12.0. Categorical variables were shown as numbers and percentages. Numeric variables with normal distribution were described as means (SD), and others as medians (minimum - maximum). The chi-square test and Fisher's test were used to compare categorical variables. The differences between the numerical variables with normal distribution were evaluated with student's t-test or ANOVA test (in the case of significant differences further subgroup analyses were performed by post-hoc analysis). The differences between the numerical variables with abnormal distribution were evaluated with either the Mann-Whitney test or the Fisher test. To establish correlations between variables, the Pearson test and Cramer's V were used. A p-value of <0.05 was considered as statistically significant.

Results

Out of 83 patients with newly diagnosed T1DM included in the study, 38 (45.8%) were females and 45 (54.2%) were males. The mean age at onset of the disease was 8.40 years (median 8, range 1.58 -17.75 years). The features of the study group by age subgroups and gender are shown in Tables 1 and 2.

At the time of diagnosis, 31 of the 83 patients (37.3%) were younger than 5 years, 23 patients (27.7%) were between 6 and 10 years, and 29 patients (34.9%) were between 11 and 18 years. The peaks of onset of diabetes occurred in two age groups: 2–4 years and 12–14 years (Fig. 1).

The mean duration of symptoms in the total study group was 21.96 days (median 14, range 0-180 days). A significantly longer

Table 1. Characteristics of the entire study group and comparison of age subgroups

Characteristics	Groups of participants				P
	Total (n/%)	≤5 years (n/%)	6-10 years (n/%)	≥11 years (n/%)	
	(83/100)	(31/37.3)	(23/27.7)	(29/34.9)	
Age at diagnosis (years)	8.40±4.82	3.27±1.30	8.37±1.47	13.9±1.96	-
Gender (girls/boys; %)	45.8/54.2	48.4/51.6	52.2/47.8	37.9/62.1	0.553
Family history of T1DM (%)	9.64	6.45	8.69	13.79	0.619
Duration of symptoms (days)	21.96±27.92	12.77±9.55	15.22±10.19	37.14±41.64	0.016
Polydipsia (%)	90.36	90.32	86.96	93.1	0.757
Polyuria (%)	90.36	90.32	86.96	93.1	0.757
Weight loss (%)	49.39	51.61	43.48	51.72	0.800
Polyphagia (%)	16.86	16.13	21.74	13.79	0.742
Fatigue (%)	12.05	12.9	8.7	13.79	0.840
Frequency of DKA /severe DKA (%)	25.3/6.02	38.71/12.9	17.39/0	17.24/3.45	0.095/0.110
HbA1c (%)	11.31±2.12	10.37±1.95	11.56±1.69	12.12±2.26	0.0039
ICA (%)	84.34	83.87	91.3	79.31	0.164
GAD Ab (%)	68.67	67.74	78.26	62.07	0.158
IA2 Ab (%)	59.04	64.52	52.17	58.62	0.139
Positive thyroid Ab (%)	13.25	6.45	17.39	17.24	0.369
Positive t-TG Ab (%)	6.02	6.45	8.7	3.45	0.726

DKA=Diabetic ketoacidosis; HbA1c=Glycosylated hemoglobin; ICA=Islet cell antibodies; GAD=Aanti-glutamic acid decarboxylase; Ab=Autoantibodies; IA2=Tyrosine phosphatase islet autoantibodies; t-TG Ab=Tissue transglutaminase antibodies.

Table 2. Characteristics of the entire study group and comparison between boys and girls

Characteristics	Total (n=83)	Girls (n=38)	Boys (n=45)	P
Age at diagnosis (years)	8.40±4.82	8.05±4.85	8.70±4.82	-
Family history of T1DM (%)	9.64	10.52	8.89	0.459
Duration of symptoms (days)	21.96±27.92	20.21±20.36	23.44±33.15	0.6231
Polydipsia (%)	90.36	89.47	91.11	1.000
Polyuria (%)	90.36	89.47	91.11	1.000
Weight loss (%)	49.40	55.26	44.44	0.381
Polyphagia (%)	16.86	18.42	15.55	0.775
Fatigue (%)	12. 05	13.16	11.11	1.000
Frequency of DKA /severe DKA (%)	25.3/6.02	21.05/2.63	28.89/8.89	0.456/0.368
HbA1c (%)	11.31±2.12	11.29±2.13	8.8±4.72	0.945
ICA (%)	84.34	92.1	77.78	0.056
GAD Ab (%)	68.67	78.95	60.0	0.054
IA2 Ab (%)	59.04	68.42	51.11	0.113
Positive thyroid Ab (%)	13.25	13.16	13.33	1.000
Positive t-TG Ab (%)	6.02	5.26	6.67	1.000

DKA=Diabetic ketoacidosis; HbA1c=Glycosylated haemoglobin; ICA=Islet cell antibodies; GAD=Anti-glutamic acid decarboxylase; Ab=Autoantibodies; IA2=Tyrosine phosphatase islet autoantibodies; t-TG Ab=Tissue transglutaminase antibodies.

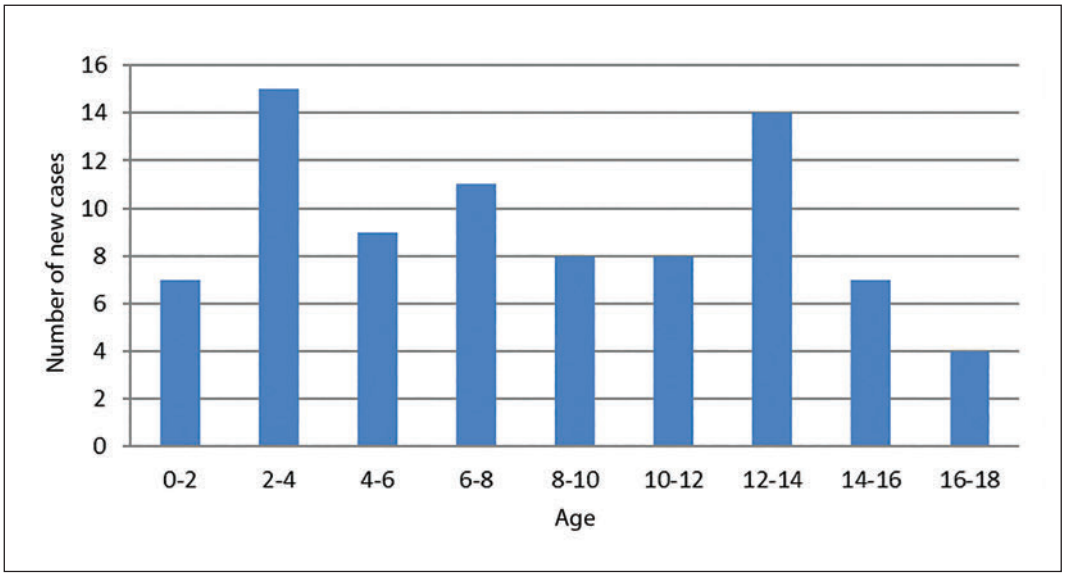

Fig. 1. *Distribution of newly-diagnosed children with T1DM by age.*

duration of symptoms was observed in the ≥11 years subgroup (P=0.0116). The most common initial symptoms were polyuria and polydipsia, which were observed in 90.36% patients. Symptoms did not differ by gender or age. DKA at the time of diagnosis was present in 21 (25.3%) patients. Severe DKA was found in 6%, moderate in 7.23%, and mild in 12.05% of our patients respectively. There were no significant differences in frequency of DKA between the gender and age subgroups.

In 9.64% cases the family history of diabetes among first-degree relatives was positive. In all children with a family history of diabetes the disease was detected before the development of DKA. There was a weak correlation between positive family history and DKA at the time of diagnosis (Kendal tau -0.1901). In patients with a family history, the duration of symptoms before T1DM was diagnosed was in the range of 0-90 days. There was no statistically significant correlation between positive family history and duration of symptoms (Kendal tau -0.0660, P=0.3718).

The mean HbA1c level of the total study group was 11.31±2.12%. In 72.28% newly diagnosed cases HbA1c was >10%, in 21.69% it was between 8-10% and in 6% it was between 6-8% respectively. The HbA1c level was significantly higher in the ≥11 years subgroup compared to the ≤5 years subgroup (P=0.0039). Of the total patients, 30.1% were diagnosed in autumn, 24.1% in spring, 22.9% in winter, and 22.9% in summer. Data on GAD Ab, ICA and IA-2 Ab were available in 80 cases. No immunological markers of beta-cell autoimmunity were found in 5 patients (6.25%). Anti-thyroid antibodies were found in 11 (13.25%) cases, in 6 boys and 5 girls. Positive t-TG Ab was detected in 5 (6.02%) patients. In all children with increased t-TG Ab antibodies celiac disease was confirmed by intestinal biopsy. Anti-thyroid and t-TG Ab positivity did not differ by gender or age subgroups.

Discussion

T1DM is one of the most common chronic metabolic diseases in children and adoles-

cents. Approximately 80,000 children under 15 years are estimated to develop T1DM annually worldwide (14). There are significant differences in the incidence of T1DM in different countries, within countries and among different ethnic groups. The incidence of T1DM is highest in Finland and Sardinia (37 to 65/100,000 children younger than 15 years) and lowest in China and Venezuela (0.1 to 0.5/100,000 children) (15, 16). During the 2004-2012 period, the incidence of T1DM among Croatian children under 14 years of age was 17.23/100,000/year. The annual increase rate for this period was 5.87%. The incidence of T1DM increased in this period compared with the incidence in 1995 to 2003 and places Croatia among countries with a high risk for T1DM (17).

The age of presentation of childhood onset T1DM has a bimodal distribution. The first peak between 4 and 6 years of age is a result of the increased frequency of infections. The second peak in early puberty occurs as a result of pubertal stress, related to insulin antagonism of growth hormones and gonadal hormones (3). In our study the first peak was noticed in the age group between 2 and 4 years. This was followed by a second peak in the 12 to 14 years age group. Our results suggest that the incidence of T1DM in children younger than 5 years has been increasing. This finding is consistent with the results of other studies (6, 15), but it differs from the report by Rojnic Putarek et al. (17) where no increase was found in the youngest age group of children. Although most autoimmune diseases more commonly affect females, there appears to be no gender difference in the overall incidence of childhood T1DM. However, a male gender bias was mainly observed in older adolescents and young adults (18-20). In our study T1DM affected 54% boys and 46% girls. Although boys were more often affected than girls in the ≥11years subgroup, no significant difference was determined. Most cases of T1DM occur sporadically in the absence of a family history of diabetes. We found a family history of T1DM in first-degree relatives in 9.64% of the patients. These results are similar to those reported by other authors (3, 21). The mean duration of symptoms in our patients before establishing the diagnosis was approximately 3 weeks. Our results regarding the duration of symptoms were similar to those reported by some authors (3, 22, 23), although there are studies in which the symptoms are present for a much shorter period of time (24, 25). In our study, significantly longer duration of symptoms and higher values of HbA1c were reported in the ≥11 years subgroup. Childhood and adolescence are periods of life when children tend to avoid parental control and detection of symptoms may be difficult or delayed.

New patients most often presented with polyuria (90.36%), polydipsia (90.36%) and weight loss (49.39%). The most serious, life-threatening presentation of T1DM is DKA, which is a result of absolute insulin deficiency. The incidence of DKA at presentation of T1DM diagnosis differs greatly, ranging from 15% to 67% (23, 26, 27). Although the incidence of T1DM has been increasing worldwide, the incidence of DKA at presentation has decreased or has not changed (28). In countries with a higher incidence of T1DM, which are also those with a high standard of living, better health care and management of the disease, the proportion of patients presenting with DKA is smaller (22, 23, 29, 30). Also, a family history of diabetes is associated with a reduced risk of DKA at T1DM diagnosis. However, medical staff play a crucial role in the prevention of DKA. The risk of DKA increases significantly in cases when diabetes is not diagnosed on the first visit to the physician (31). In our study, 25.3% of patients had DKA. The incidence of DKA was not significantly higher than in

other countries. Severe DKA was seen in 6% of our cases. Although in all children with a family history of diabetes, the disease was discovered before development of DKA, there was no significant impact of family history on the incidence of DKA. These results were similar to the results of Demir et al. (3). In our study a relatively higher ratio of DKA in younger children was noticed, but the difference was not significant. A younger age at T1DM diagnosis, particularly <2 years, is a risk factor for DKA (29). In our study, in 35.5% of children younger than 5 years DKA was the initial symptom, and 54.5% of these were children under the age of 3 years. Seasonal variation of diagnosis of T1DM has been suggested in most studies, with a higher reported incidence of T1DM in colder as compared to warmer months. We found that the diagnosis of T1DM was most frequent in winter and spring. However, some authors have reported higher rates of presentation in winter exclusively (3, 7), while others reported spring or summer as the most common seasons of T1DM diagnosis (3, 8, 16). The presence of GADAb, IA2Ab, ICA and/or zinc transporter 8 protein in the blood of patients with T1DM proves the autoimmune pathogenesis of β-cell destruction. Positive GAD Ab was reported in 52-80%, IA2 Ab in 50-63%, and ICA in 70-80% of cases with recent-onset of T1DM (31, 32). Our results are in accordance with other studies. GAD Ab is less frequent among boys with newly-diagnosed diabetes before the age of 10 years (32)**.** In our study, positive ICA and GAD Ab were more often reported in girls, but with a low significant difference. T1DM is associated with an increased risk of developing other autoimmune diseases as a result of genetic susceptibility to autoimmune diseases. The most common comorbidities include: autoimmune thyroid disease (15-30%), celiac disease (4-9%), autoimmune gastritis/pernicious anaemia (5-10%), vitiligo (2-10%), and Addison's disease (0.5%) (32). At the time of diagnosis, 17-25% of patients, primarily females, had increased anti-thyroid antibodies (33-36). In our study, 13% of new cases had elevated anti-thyroid antibodies and 6% had increased t-TG Ab antibodies, equally boys and girls.

Limitation of study

This study had some limitations, including the fact that it was a retrospective medical record review. Furthermore, the study was limited by the small sample size stemming from the collection of data in a single centre. So, a multi-centre study is needed to evaluate the epidemiological features of T1DM in Croatian children.

Conclusion

Our study shows that the age at T1DM onset has been decreasing. At diagnosis, in older children symptoms had lasted significantly longer and mean HbA1c levels were significantly higher. The incidence of DKA in children with newly diagnosed T1DM is still high and includes one quarter of all patients. It is necessary to raise the awareness of medical staff and the public for early recognition of the symptoms of diabetes.

Authors' contributions: Conception and design: SS and IBA; Acquisition, analysis and interpretation of data: IBA, DS, and SS; Drafting the article: IBA; Revising the article critically for intellectual content: IBA, SS, and DS; Approved final version of the manuscript: SS, and IBA.

Conflict of interest: The authors declare that they have no conflict of interest.

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