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VISOKA PREVALENCIJA DIJABETESNE KETOACIDOZE KOD MLADIH SA NOVOOTKRIVENIM TIPOM 1 DIJABETESA MELITUSA U BEOGRADU: DESETOGODIŠNJE ISKUSTVO TERCIJERNOG CENTRA

HIGH PREVALENCE OF DIABETIC KETOACIDOSIS IN CHILDREN WITH NEWLY DIAGNOSED TYPE 1 DIABETES IN BELGRADE, SERBIA: 10-YEAR TERTIARY CENTRE EXPERIENCE

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SAŽETAK

SUMMARY

Uvod/cilj: Dijabetesna ketoacidoza (DKA) je najznačajniji uzrok mortaliteta mladih sa tipom 1 dijabetesa melitusa (T1DM). Rezultati poslednjih istraživanja ukazuju na zabrinjavajuće visoku prevalenciju DKA u trenutku postavljanja dijagnoze T1DM kod mladih u Beogradu. Cilj ovog istraživanja bila je procena učestalosti DKA kod dece i adolescenata sa novootkrivenim T1DM tokom desetogodišnjeg perioda u tercijernom centru u Beogradu.

Metode: Podaci su prikupljeni retrospektivnom pretragom medicinske dokumentacije sve dece i adolescenata sa novootkrivenim T1DM koji su bili hospitalizovani u našem centru tokom perioda od 1. januara 2007. godine do 1. januara 2017. godine.

Rezultati: Dijagnoza novootkrivenog T1DM postavljena je kod ukupno 501 deteta (233 devojčice i 268 dečaka) prosečnog uzrasta 9.55 ± 4.26 godina, sa prosečnom vrednošću pH od 7.28 ± 0.14 (6.78-7.51) u trenutku postavljanja dijagnoze. Devojčice sa T1DM su u proseku bile mlađe u odnosu na dečake (9.05 ± 4.04 god. u odnosu na 9.98 ± 4.41 god, respektivno, $p < 0.05$). Od ukupnog broja pacijenata, 191 (38,1%) je u trenutku postavljanja dijagnoze imao DKA, od čega je 47.6% bilo u blagoj, 26,2% u umerenoj, a 26,2% u teškoj ketoacidozi. U grupi mlađe dece, uočena je veća učestalost DKA (40%) u odnosu na grupu dece uzrasta > 11 godina (35%), ali ova razlika nije bila statistički značajna.

Zaključak: Rezultati ukazuju na zabrinjavajuće visoku prevalenciju DKA u trenutku postavljanja dijagnoze T1DM kod mladih u Beogradu, bez značajne razlike u odnosu na uzrast. Ovi nalazi ukazuju na potrebu

Introduction/Aim: Diabetic ketoacidosis (DKA) is one of the most important causes of acute mortality in youth with type 1 diabetes mellitus (T1DM). Recently published data suggested worryingly high frequency of DKA at the onset of T1DM in Belgrade youth. The goal of this study was to assess the frequency of DKA at the onset of T1DM and the associated risk factors in Belgrade youth during the previous 10 years at a tertiary centre.

Methods: Data were collected retrospectively from the medical records of all children with new-onset T1DM admitted to our centre during the study period between 1st January 2007 and 1st January 2017.

Results: During the study period, a total of 501 subjects (233 girls and 268 boys) were diagnosed with new-onset T1DM, with a mean age of 9.55 ± 4.26 years, and mean pH at the time of diagnosis of 7.28 ± 0.14 (6.78-7.51). Girls with T1DM were younger compared to boys (9.05 ± 4.04 years vs. 9.98 ± 4.41 years, respectively, $p < 0.05$). Of all patients, 191 (38.1%) presented with DKA, 47.6% of which were classified as mild, 26.2% as moderate and 26.2% as severe DKA. Slightly higher frequency of DKA was noticed in the younger age groups (40%) compared to the children > 11 years (35%), although this difference was not statistically significant.

Conclusion: There is an alarmingly high rate of DKA at the onset of T1DM in Belgrade youth with no significant differences between different age groups. These findings emphasize the need for intensive public health preventive actions aimed at early diagnosis of T1DM in all age groups.

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za intenzivnim javno-zdravstvenim merama prevencije ketoacidoze, odnosno pravovremenog postavljanja dijagnoze T1DM kod dece i adolescenata u Beogradu.

Ključne reči: Dijabetesna ketoacidoza, dijabetes melitus tipa 1, deca, prevencija, epidemiologija

Keywords: Diabetic ketoacidosis, type 1 diabetes mellitus, children, prevention, epidemiology

Introduction

Diabetic ketoacidosis (DKA) is one of the most important causes of acute mortality in youth with type 1 diabetes mellitus (T1DM) (1,2). The frequency of DKA at the time of diagnosis of T1DM is highly variable, with worldwide reported incidences ranging from 12.8 to 80% (3-18).

Serbia has a population of children under the age of 19 years of 1,427,272, and a large proportion of youth (317,258 - 22%) lives in Belgrade, the capital city (19). There are two tertiary paediatric centres in Belgrade with paediatric endocrinology departments and intensive care units in which the children with newly diagnosed T1DM are treated: the University Children's Hospital, and our hospital the Mother and Child Healthcare Institute of Serbia "Dr Vukan Cupic" (18). Besides those residing in Belgrade, children from other parts of Serbia are also frequently being referred to these two centres in Belgrade at the time of diagnosis due to the lack of resources in other regions.

The recently published data from the University Children's Hospital in Belgrade, the other tertiary centre from Belgrade, revealed alarmingly high frequency of DKA (32.9%) in youth with newly diagnosed T1DM during the period 1991-2011, with DKA frequency up to 55% in children younger than 5 years (18). Considering that such high prevalence of DKA in children and adolescents with newly diagnosed T1DM represents a worrisome and significant public-health issue, we analyzed the medical records of patients diagnosed at our centre in order to provide a comprehensive insight into the frequency of DKA in youth with newly diagnosed T1DM living in the Belgrade area.

The aim of the present study was to analyze the frequency of DKA and the associated risk factors at the time of onset of T1DM during the period of the past 10 years (2007-2017) at our hospital, the other tertiary centre in Belgrade, Serbia.

Methods

The data were collected retrospectively from the medical records of all children with new-onset T1DM admitted to the Mother and Child Healthcare Institute of Serbia "Dr Vukan Cupic" during the study period between 1st January 2007 and 1st January 2017. Subjects with other types of diabetes were excluded from this study. Data regarding patients' gender, age at diagnosis, duration of symptoms, blood pH (or serum bicarbonates when pH was unavailable), glucose and blood glycosylated haemoglobin (HbA1c) level at the time of diagnosis were collected retrospectively from the medical records. Study protocol was approved by the Hospital Ethics Committee and was in accordance with the Declaration of Helsinki.

The final study cohort included 501 patients (233 girls and 268 boys) with newly diagnosed T1DM. The patients were classified into three age groups: under 5 years, 5-11 years and > 11 years. Based on the date of admission, the study period was also stratified into two 5-year periods.

The diagnosis of DKA was based on ISPAD 2014 guidelines: hyperglycaemia (blood glucose > 11 mmol/L) with acidosis (venous pH < 7.3 or bicarbonate < 15 mmol/L), and with ketonaemia or ketonuria (20). DKA severity was also categorized according to the ISPAD 2014 guidelines as mild (venous pH < 7.3, bicarbonate < 15 mmol/L), moderate (pH < 7.2, bicarbonate < 10 mmol/L) or severe (pH < 7.1, bicarbonate < 5 mmol/L) (20).

Differences in the means between groups were tested using the independent t-test, Mann-Whitney U test and Kruskal-Wallis independent samples test, depending on the number of groups and the distribution of the variables, and the Pearson's chi-square test was used for categorical variables. P-values < 0.05 were considered as statistically significant. Analyses were conducted using the SPSS version 20 (SPSS Inc, Chicago, IL) statistical software.

Results

Of all 501 patients with T1DM, 191 (38.1%) presented with DKA and 310 (61.9%) without DKA (Table 1). DKA was present at the time of diagnosis slightly more often in newly diagnosed girls (40.8%) compared to boys (35.8%); however, the difference was not statistically significant. In the group of patients without DKA, the mean age was 9.73 ± 4.26 years which was a slightly higher

than in the group with DKA 9.25 ± 4.27 . In the group of patients with DKA, mean blood glucose level was significantly higher than in the group without DKA. As expected, the mean pH among patients with DKA was significantly lower. Also, the level of HbA1c was significantly higher in the group with DKA than in the group without DKA. Patients with DKA had a slightly shorter duration of symptoms, but without statistically significant difference.

Table 1. Characteristics of patients with or without diabetic ketoacidosis*

	No DKA (Mean $\pm$ SD)	Ranges	DKA (Mean $\pm$ SD)	Ranges	p value*
N	310		191		
Age at diagnosis (years)	9.73 ± 4.26	1.24-17.72	9.25 ± 4.27	0.93-18.74	NS
Sex ratio (males %)	55.5%		50.3%		NS**
<i>Biochemical parameters</i>					
pH	7.37 ± 0.04	7.30-7.51	7.15 ± 0.12	6.78-7.29	<0.001
Glucose (mmol/L)	21.8 ± 8.6	7.3-55.0	25.5 ± 8.4	10.1-57.8	<0.001
HbA1c (%)	11.4 ± 2.2	6.3-18.9	12.2 ± 2.1	7.6-19.7	0.001
Duration of symptoms (days)	20.7 ± 21.1	0-155	21.3 ± 21.2	0-120	NS

No DKA – patients without diabetic ketoacidosis at the time of T1DM diagnosis; DKA – patients with diabetic ketoacidosis at the time of T1DM diagnosis; NS – not statistically significant; *p value according to the t test; **p value according to Pearson's chi-square test.

When subjects were compared according to DKA severity at the onset of T1DM, there were no significant differences in age at diagnosis, gender, or levels of HbA1c (Table 2). As expected, pH level ($p < 0.001$)

was significantly lower in the groups with moderate and severe DKA, and interestingly, blood glucose levels were significantly higher in the group with severe DKA ($p = 0.002$).

Table 2. Characteristics of patients with diabetic ketoacidosis (DKA) (N = 310) at time of diagnosis regarding DKA severity

	Mild DKA	Moderate DKA	Severe DKA	p value*
N (proportion of cohort)	91 (47.8%)	50 (26.2%)	50 (26.2%)	
Age at diagnosis (years)	10.0 ± 4.4	8.5 ± 3.5	8.6 ± 4.6	NS
Sex ratio (males %)	51%	50%	50%	NS**
<i>Biochemical parameters</i>				
pH	7.25 ± 0.03	7.16 ± 0.03	6.98 ± 0.07	< 0.001
Glucose (mmol/L)	23.9 ± 8.3	24.4 ± 5.8	29.4 ± 9.6	0.002
HbA1c (%)	12.4 ± 2.1	12.3 ± 2.1	11.9 ± 2.3	NS

NS – not statistically significant; *p value according to the Kruskal-Wallis independent samples test; **p value according to Pearson's chi-square test

There were 96 children (19.2%) aged less than 5 years at the time of diagnosis of T1DM (Table 3). The incidence of DKA in this age group was 40.6% ($n = 39$), without statistically significant differences in DKA prevalence in older age groups, as shown in Table 3. In the youngest age group, higher

frequency of severe DKA was observed, but also, without any statistical significance. Slightly higher levels of HbA1c were observed in older age groups. There was no significant difference in the duration of symptoms among different age groups.

Table 3. Characteristics of patients with newly diagnosed T1DM in different age groups

Characteristics	< 5 years (N=96)	5-11 years (N=198)	>11 years (N=207)	p value*
DKA at diagnosis, n (%)	39 (40.6%)	80 (40.4%)	72 (34.8%)	NS**
<i>Severity of DKA</i>				
Mild	16 (41.05%)	33 (41.3%)	42 (58.3%)	NS**
Moderate	10 (25.6%)	28 (35.0%)	12 (16.7%)	NS**
Severe	13 (33.3%)	19 (23.8%)	18 (25.0%)	NS**
<i>Laboratory findings</i>				
Blood glucose level (mmol/L)	22.5±8.6 (8.8-55.0)	22.9±7.8 (8.0-53.0)	23.8±9.5 (7.3-57.8)	NS
pH	7.27±0.16 (6.88-7.50)	7.27±0.13 (6.91 - 7.51)	7.28±0.13 (6.78 - 7.48)	NS
HbA1c (%)	10.7±1.9 (6.4-16.1)	11.7±2.2 (6.3-19.7)	12.2±2.2 (6.6-18.9)	< 0.001
Duration of symptoms (days)	16.8±17.7 (2-120)	21.7±22.9 (0-155)	22.1±20.6 (0-120)	NS

DKA –diabetic ketoacidosis; NS – not statistically significant; *p value according to the t test; NS – not statistically significant; *p value according to the Kruskal-Wallis independent samples test; **p value according to Pearson’s chi-square test.

We also compared the first half of the study period with the last 5-year period (Table 4). In 2007-2011 period, the incidence of DKA at the time of diagnosis of T1DM, as well as the percentage of severe DKA were slightly higher, but without statistically significant

difference, as shown in Table 4. Also, there were no significant differences between periods regarding the age at diagnosis of T1DM, blood glucose levels, pH or HbA1c levels.

Table 4. Comparison of children diagnosed with type 1 diabetes between 2007-2011 and 2012-2016.

Characteristics	2007-2011 (N=267)	2012-2016 (N=234)	p value
Age at diagnosis (years)	9.3±4.4 (0.9-18.7)	9.8±4.1 (1.4-18.0)	NS
Blood glucose (mmol/L)	22.9±9.0 (7.3-57.8)	23.4±8.3 (8.0-49.6)	NS
pH	7.26±0.14 (6.90-7.49)	7.29±0.13 (6.78-7.51)	NS
HbA1c (%)	11.5±2.3 (6.6-19.7)	11.9 ±2.1 (6.3-17.5)	NS
DKA n (%)	108 (40.4%)	83 (35.5%)	NS
Mild	52 (48.1%)	39 (47.0%)	NS**
Moderate	22 (20.4%)	28 (33.7%)	NS**
Severe	34 (31.5%)	16 (19.3%)	NS**

* DKA –diabetic ketoacidosis; NS – not statistically significant; p value according to t-test; *p value according to the t test; **p value according to Pearson’s chi-square test.

Discussion

Mother and Child Healthcare Institute of Serbia “Dr Vukan Cupic” is the largest paediatric hospital in Serbia and one of the two tertiary centres in the capital city Belgrade that treats children with T1DM from the Belgrade area. Considering the high prevalence of DKA at the time of T1DM diagnosis recently reported by the authors from the other tertiary

centre from Belgrade, and that such a high prevalence of DKA represents a worrisome public-health issue, this study analyzed the data from medical records of patients diagnosed at our centre, to provide a complete insight into the DKA at the onset of T1DM in children and adolescents living in Belgrade (18).

The frequency of DKA at the time of diagnosis of T1DM is known to be highly variable (3-17). In our study, 38.1% newly

diagnosed T1DM patients had DKA, which, together with the DKA incidence of 32.9% reported by the study performed at the University Children's Hospital in Belgrade, provides a complete insight and confirms the alarmingly high frequency of DKA at the time of diagnosis of T1DM in youth living in Belgrade (18). Similar worrisome DKA frequencies at T1DM onset were reported in other countries in the region, such as Croatia (31.3-41.7%) and Bosnia (48%) (21,22), although data from Montenegro showed a significantly lower incidence of 24.5% (23).

Many studies have demonstrated higher incidence of DKA at the time of T1DM diagnosis in patients aged < 5 years, with even higher rates in children younger than 2 years (17,24-27). Many authors suggest that higher incidence of T1DM in some countries is associated with a lower prevalence of DKA at the time of T1DM diagnosis, as the study from Finland that showed a relative reduction of DKA incidence over a period of 20 years, especially in the group of children younger than 5 years (28,29). However, a large study from 106 centers in Germany and Austria failed to demonstrate changes in either incidence or severity of DKA during the study period 1995-2007, while a steadily high DKA prevalence of 43.9% was observed in a study conducted on a national level in France (30,31). In the present study, although slightly higher incidence of DKA was present in younger patients, and although the prevalence of severe DKA was also higher in this age group, these findings were not statistically significant and the DKA prevalence was fairly similar among the age groups. This emphasizes the urgency of public health actions aimed at prevention of DKA, not only in the youngest age group, but among school-aged children and adolescents as well.

When two consecutive 5-year periods were compared in the present study, the number of children and adolescents with new-onset T1DM was similar. The observed mild decline in the prevalence of DKA at the time of onset of T1DM in youth from 40.4% in the first 5-year period to 35.5% in the second, together with similar findings from the previous Belgrade study, could suggest that the public awareness of the T1DM has increased over the last couple of years (18). However, the rate of DKA at onset of T1DM in Belgrade youth is still alarmingly high and suggests the fact that public health preventive programs should be implemented in order to increase public awareness of T1DM in youth, as well as awareness amongst health care

professionals.

Findings of the present study should be interpreted in the light of its acknowledged limitations. Impact of ethnicity, income status and family history were not assessed in the present study. Also, health insurance status was not assessed, though this should not have influenced findings in a significant manner, considering that free healthcare coverage is provided to all children in Serbia.

Conclusion

The presented findings confirm the alarmingly high rate of DKA at the onset of T1DM in Belgrade youth with no significant differences between different age groups. These findings emphasize the need for intensive public health preventive actions aimed at early T1DM diagnosis in all age groups, including school-aged children and adolescents, to reduce the rate of DKA, a potentially fatal T1DM complication.

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