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Original Research Article

Stable rates of diabetic ketoacidosis at the initial episode of type 1 diabetes mellitus are associated with a shift towards younger age at diagnosis: 8 years' experience of a large Portuguese centre

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ABSTRACT

Background: The rate of diabetic ketoacidosis in new-onset type 1 diabetes mellitus depends on multiple factors and is very heterogeneous between countries. An inverse relationship between the incidences of T1D and DKA seems to exist. Moreover, DKA is reported to be more common in children under 5 years old. Current data on Portuguese pediatric DKA incidence in new-onset T1D is limited. We aimed to determine the rate of DKA incidence in this population, as well as risk and protective factors.
Methods: Review of data from children aged 18 years or younger with new onset T1D, referred to a pediatric endocrinology unit between January 1st, 2013 and December 31th, 2020 (8 years).
Results: 276 patients were included with a median age of 9.6 years-old (0.5-17.9 years): 15,6% aged between 2 and 5 years-old and 3,6% under two years. A mean incidence of 34,5 new cases per year was observed, with an upward trend. One hundred and five (38%) presented with DKA, which was considered severe in 9,4%; 50 patients (18,1%) presented only with hyperglycemia. Non-DKA at presentation was associated with family history of T1D (p=0.016). DKA at presentation was more frequent in the age group under 2 years old (p=0.005).
Conclusions: DKA's frequency at new onset T1D is still high, although only a small proportion of cases was considered severe. A family history of T1D correlated with a non-DKA presentation, while an age under 2 years presented as a risk factor for DKA.

Keywords: Type 1 diabetes, Diabetic ketoacidosis, Incidence trend, Risk factors

INTRODUCTION

Type 1 diabetes mellitus (T1D) is characterized by chronic immune-mediated destruction of pancreatic β-cells leading up to insulin deficiency.[1] It has been well-accepted that the disease becomes clinically symptomatic when 90% of the β-cells are destroyed and progresses to diabetic ketoacidosis (DKA) when diagnosis is delayed. According to the International Society for Pediatric and Adolescent Diabetes 2018 consensus, DKA is classified into three categories of severity: mild, moderate and severe, based on pH and $HCO3^-$ status at diagnosis.[1]

Several risk factors for DKA at presentation have been described in the literature, which include individual factors (age, ethnicity, family history of diabetes and body mass index), family factors (parental education, health insurance status and family income), physician factors (delayed diagnosis, diagnostic error, delayed treatment), disease factors (pattern and frequency of symptoms, preceding infection), as well as other factors, such as background incidence of T1D.[2]

Globally, the rate of DKA in new-onset T1D is very heterogeneous, varying between 13 to 80%.[3] Some reports suggest an inverse correlation between DKA frequency and T1D incidence.[3,4] DKA has also been reported to be more common among young children, specially under two-years old.[5] Although DKA mortality in developed countries is less than 1%, it remains a clinical condition that can deteriorate rapidly and be responsible for cognitive complications, while also being associated with a poor long term glycemic control.[6,7] Moreover, previous studies showed that increased awareness of TD1 symptoms may promote earlier diagnosis and, therefore, reduce DKA frequency.[8] Current data on the incidence of DKA at T1D onset in Portuguese pediatric population is limited.[9] In this study we aimed to analyze the clinical and biochemical status of children and adolescents with newly diagnosed T1D, to determine the rate of DKA's incidence and to identify factors associated with the development of DKA at T1D diagnosis in children and adolescents referred to our center.

METHODS

Retrospective study performed in a pediatric endocrinology unit of a level III hospital (Hospital D. Estefânia, Centro Hospitalar Universitário Lisboa Central, Portugal) that included children under 18 years with new onset T1D, from 01 January, 2013 to 31 December, 2020 (eight years duration). T1D was established based on the usual diagnostic criteria and the presence of pancreatic autoantibodies.[1] Patients with incomplete information regarding presentation status, namely pH and serum bicarbonate, were excluded.

Data was collected from the electronic clinical files and included: age at presentation; gender; co-morbidities; family history of type 2 diabetes mellitus (T2D), T1D or other autoimmune disease; symptoms and their duration; blood glucose, ketonemia, pH, bicarbonate and HbA1C at presentation; and type of hospitalization ward/pediatric intensive care unit (PICU). Clinical presentation of T1D was categorized as: hyperglycemia, hyperglycemia with ketonemia (≥6 mg/dl), and DKA. DKA was classified as: mild (pH <7,3 and/or bicarbonate <90 mg/dl), moderate (pH <7,2 and/or bicarbonate <60 mg/dl), and severe (pH <7,1 and/or bicarbonate <30 mg/dl).

Data was analysed using SPSS, 21th version software (SPSS, Chicago, IL) for Mac. Continuous data were compared by use of paired and unpaired Student t test whenever applicable. Independent proportions were compared by use of the 2-tailed Fisher exact test. A p value of 0.05 was used as the threshold of significance. Data is presented as median (min-max), unless stated otherwise.

RESULTS

Our study included 291 patients with a new diagnosis of T1D, of whom 276 met the inclusion criteria (15 patients were excluded because of missing/incomplete data). A mean incidence of 34,5 new T1D cases per year was observed (Figure 1), with an upward trend throughout the study period.

The median age at diagnosis was of 9,6 years (0.5-17.9 years), with a slight male predominance (56.5%). There was no significant difference between genders in age at presentation. The peak incidence was observed amongst the group of patients aged 10 to 14 years (36.2%), followed by the age group of five to nine years (33.3%). 15,6% patients were between two to five years old and 3,6% were under two. Comparing 2013 to 2020, new onset T1D cases under five years more than tripled (n=3 vs. n=10) (Figure 2). Almost a third (28.6%) had family history of autoimmune diseases. While 15.4% had family history of T1D, 36.8% of patients had family history of T2D. Demographic data is summarized in (Table 1).

Table 1: Demographic characteristics of the study population.

Parameters	Overall	Non-DKA	DKA	P value
Total N (%)	276	171 (61.9)	105 (38.0)	
Gender, N (%)				
Female	120 (43.5)	79 (46.2)	41 (39.0)	NS
Male	156 (56.5)	92 (53.8)	64 (61.0)	
Age group, mean (SD), (years)				
<2	10 (3.6)	2 (1.2)	6 (7.6)	0.005
≥2-5	43 (15.6)	31 (18.1)	12 (11.4)	NS
≥5-10	92 (33.3)	54 (31.6)	38 (36.2)	NS
≥10-15	100 (36.2)	69 (40.4)	31 (29.5)	NS
≥15	31 (11.2)	15 (8.8)	16 (15.2)	NS

DKA: diabetic ketoacidosis; NS: non significant; SD: standard deviation.

In 29.3% of patients, the duration of symptoms was between two and four weeks. While the majority (50,8%) of patients presented symptoms for two weeks to two months, presentation with symptoms duration over two months declined through the study period, from 20% in 2013 to just 4.5% in 2020. Interestingly, 25% of patients presented symptoms for less than a week in 2020, versus 10.5% in the eight-year period. Patients presented mainly polydipsia (83.7%), polyuria (81.2%) and weight loss (67.8%). The frequency of symptoms was similar between age groups with exception to secondary enuresis, which occurred in 14.9% of patients, mainly in children aged five to nine years old (28.4%).

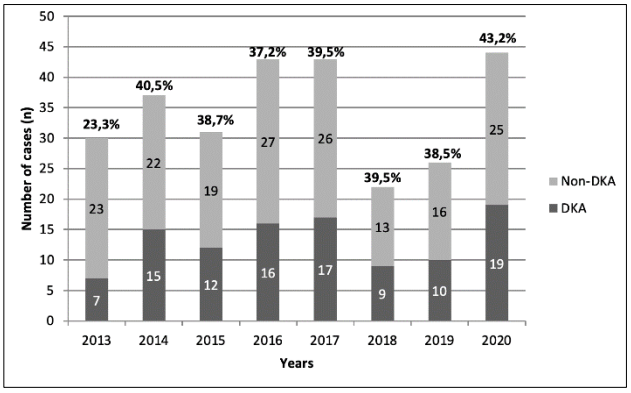

Figure 1: Type 1 DM's annual incidence throughout the study period.

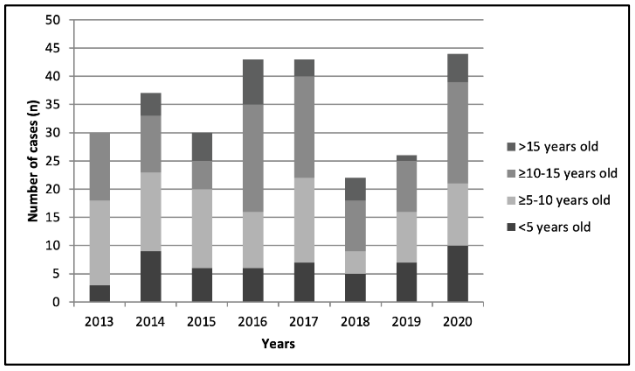

Figure 2: Age group's distribution of new onset T1D.

Twenty patients (7.2%) were admitted to the PICU: 16 for severe DKA (seven of which with an altered mental status), three for young age (<two years old) and one for moderate DKA with severe hyponatremia. The mean blood glucose and HbA1C at diagnosis were 410 mg/dl (200-980 mg/dl) and 11,0% (6.3-17.9%), respectively. Total 105 patients (38%) presented with DKA, increasing from 23.3% in 2013 to 43.2% in 2020. Hyperglycemia with ketosis was the most frequent form of clinical presentation (43.8%); 50 patients (18.1%) presented only with hyperglycemia (Figure 3). DKA was severe in 9.4% of cases. Yearly, severe DKA reached a maximum frequency of 20.5% in 2020. Non-DKA at presentation was significantly associated with family history of T1D (p=0.016). DKA presentation, on the other hand, was more frequent in children under two years old (p=0.005). Gender, family history of diabetes type 2 or other autoimmunity, symptom duration and higher HbA1c were not statistically associated with DKA.

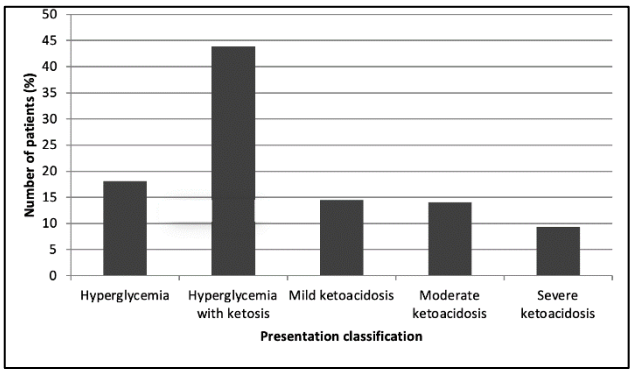

Figure 3: Classification of presentation.

DISCUSSION

In recent decades, a rise in T1D has been observed worldwide, mainly in developing countries.[10] This increase parallels a decrease in the relative contribution of highest risk HLA genotype, suggesting an increasing role for environmental factors in T1D's etiology.[11] Nevertheless, in some countries the incidence of T1D appears to have plateaued.[12,13]

In Portugal, according to the national register DOCE 2000-15 report, the overall T1D's annual incidence increased until 2008, subsequently remained stable until 2013 (17.2-18.7 new cases under 19 years-old per 100.000 habitants) and decreased since then, accounting an annual incidence of 11.5 in 2015. However, an upward trend was observed in the present study. These opposite results may be explained by a possible national underestimation, as diagnosis notification this register is not mandatory.

Although T1D's peak incidence has classically been described between the age of 10-14 years, a recent report using a 15 year database from 19 European countries revealed an annual rate increase of 5.4, 4.3 and 2.9 percent for the age groups of 0 to 4 years, 5 to 9 years and 10 to 14 years respectively.[15,19,9] Similarly, our study showed a higher incidence in younger ages (5-10 years). Likewise, if this trend continues, the number of new T1D cases in children younger than five years of age will be expected to double in some regions until 2020, and to rise by 70 percent for prevalent cases younger than 15 years.[9] Moreover, although no consistent age trend was observed, which was expectable given the short study period, it is noteworthy that, comparing 2013 with 2019, a 2.3% annual incidence increase was observed in the group under five years old. This shift towards younger age has also been observed in recent studies.[17]

DKA frequency at T1D presentation has a wide geographic variation.[4,18,19] Indeed, an updated systematic review and meta-analysis reported the lowest rate in Denmark (14,7%) and the highest in Saudi Arabia (79,8%).[20] In the present study, DKA's incidence rate was of approximately 38%, similar to that of countries like Croatia (36,4%), Austria (37,2%), Spain (39,5%), Iceland (36%) and the Unites States of America (38,9%).[21-25] Although comparable, the overall incidence rate remains unacceptably high.

A state of emergency due to the COVID-19 pandemic was declared on March 14th 2020 by the Portuguese government. From that date on, 31 cases of T1D were reported. Although the cases that were diagnosed during the first wave of the pandemic are featured, its direct impact comparatively to pre-pandemic years was not the aim of this study and, as such was not assessed. Other countries reports have also showed a significant rise of DKA in new-onset T1D cases in 2020, raising concerns about how both lockdowns and SARS CoV-2 may have interfered with DKA incidence.[26]

Although a variety of symptoms may accompany T1D onset, polyuria, polydipsia, and weight loss are the most frequent symptoms described, in agreement with the findings of this study. In children under 10 years, secondary enuresis is also an important and often under looked symptom.[27,28] The duration of symptoms prior to diagnosis varies largely from few days to several weeks. In our cohort, only 23,3% had a duration of symptoms less than two weeks, and the majority were diagnosed after two to four weeks of symptoms, as reported in other studies.[4,29] In this study, positive family history of T1D correlated negatively with DKA. It is well documented that a first-degree relative with T1D decreases the risk of DKA at diagnosis, probably due to increased awareness among these families, rather than an increased genetic risk predisposing to a milder onset of disease.[30]

We also found higher rates of DKA in children under 2 years old. Concerning age, several studies reported an increased risk of DKA at diagnosis in children under five years, particularly those under two years. This aspect is probably multifactorial. Clinicians may have a lower index of suspicion in this age group as symptoms, namely polydipsia, polyuria and enuresis, are more difficult to recognise.[31] Previous successful campaigns targeting parents, schools and primary healthcare professionals have been able to reduce DKA's incidence. Moreover, recent studies have pointed out that a specific pattern of insulitis may confer young children with a more aggressive T1D endotype, characterized by more severe β cell destruction.[31-34] The small cohort size is the primary limitation of this study, mitigating the power of its results. The fact that there was no control group or a historic cohort to determine an evolution trend, are also major limitations. Nevertheless, other authors have also pointed these drawbacks. On another hand, this is not a population-based study and our results may vary from the overall pediatric Portuguese T1D epidemiology. Therefore, a multicenter study or even a national study is warranted in order to determine DKA rates and its risk factors.

CONCLUSION

To conclude, this retrospective review shows an upward trend in T1D's incidence in children under five years old and a high DKA rate at disease onset, which was more frequent in patients under two years of age. These findings support previous reports that suggested young age could be a risk factor for DKA at T1D diagnosis. Furthermore, even though it's limited to a single centre, our data contributes to the unveiling of the relatively obscure landscape encompassing the characteristics of T1D onset in the Portuguese pediatric population. It is urgent to promote an earlier diagnosis through the implementation of educational programmes that will contribute to improve awareness for pediatric T1D.

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