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CLINICAL PRESENTATION OF TYPE 1 DIABETES MELLITUS AND FACTORS ASSOCIATED WITH DIABETIC KETOACIDOSIS (DKA) IN CHILDREN AND ADOLESCENTS AT DAVID BERNARDINO NATIONAL PEDIATRIC HOSPITAL- LUANDA ANGOLA

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ABSTRACT

Introduction: Type 1 (T1DM) is caused by an absolute deficiency of insulin due to the progressive destruction of the beta cells of the pancreas. The incidence of T1DM varies sharply across countries and age groups; with the highest incidence observed in children between 10 and 14 years old. The diagnosis of Diabetes is made in a symptomatic individual presenting with polydipsia, polyuria, polyphagia, weight loss and a fasting blood glucose concentration > 126 mg/dl (7 mmol/l), a random blood glucose level > 200 mg/dl (11.1 mmol/l) or glycosylated haemoglobin (Hb A1C) > 6.5%. The diagnosis of diabetic ketoacidosis (DKA) should be considered in any patient presenting with (glycaemia > 200 mg/dl), arterial pH <7.3 or bicarbonate level < 15 mmol/l and ketonemia (ketonuria). DKA as the first clinical presentation of T1DM is persistently frequent in Africa. ***Objective:*** To describe the clinical presentation of T1DM and factors associated with DKA in children and adolescents aged 6 months to 19 years, followed up in the Endocrinology clinic at Paediatric Hospital David Bernardino (HPDB) in Luanda Angola. ***Methodology:*** A cross-sectional, hospital-based study was carried out in children and adolescents at David Bernardino paediatric Hospital – Luanda, Angola ***Results:*** Of the 80 patients studied, 43 (53.5%) were female and 37 (46.5%) were male. The median age of the studied participants was 11.9±4.1 years (minimum of 7 months and a maximum of 18 years); while the median age at diagnosis was 9.3± 4.1 years (minimum of 6 months and maximum of 16 years). The classic signs of presentation of diabetes were: polyuria in 97.5%, polydipsia in 87.5% and loss of weight in 82,5%. Of the subjects studied, 52.5% had DKA at the time of T1DM1 diagnosis. After successful iterations at the multivariable modelling, the significant predictors for DKA at diagnosis of T1DM were: Absence of family member with diabetes, especially aunt with diabetes (p=0.035), no family member on insulin therapy (p=0.031), and caregiver's level of education (p=0.058). ***Conclusion:*** Very high number of patient present with DKA at the time of diagnosis. Significant predictors for DKA at diagnosis of TIDM in children seen in the endocrinology clinic at HPDB were: Age at diagnosis, absence of family member with diabetes, especially aunt with diabetes, none family member on insulin therapy, and caregiver's level of education.

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INTRODUCTION

Diabetes Mellitus is a disorder of the metabolic homeostasis controlled by the beta cells hormone, Insulin, leading to the abnormal metabolism of carbohydrate, proteins and fat. Type 1 Diabetes Mellitus (T1DM) is caused by an absolute insulin deficiency due to progressive destruction of the beta cells of the pancreas. It is now recognized that type 1 diabetes is not a single autoimmune disease but a complex interplay between genomes, environment, metabolism and the immune system that can be different from one person to another.

The prevalence of TIDM has be shown to be around 30 million patients in the world with an incidence varying by country, and even by region within the same country[1]. This incidence of TIDM in children has been estimated to be between 1.9 per 100,000 person years in China, to 52.2 per 100,000 in Finland [1].

In Africa, the incidence was estimated to be between almost 1/100.000 children per year in Ethiopia and Mali to around 10/100.000 children per year in libya[1]. To our best knowledge there is no study conducted in Angolan children with T1DM. Most cases of T1DM will present the classical triad of polyuria, polydipsia and polyphagia, as shown by Ibekwe in a study conducted in Nigeria[2]. But almost one third of patient will present in diabetic ketoacidosis and unfortunately this number is higher in country with low prevalence of type 1 diabetic and it still showing an increasing trend in Africa[3]. The frequency of Diabetes Ketoacidosis (DKA) at diagnosis of type 1 diabetes varies from country to country and have been estimated by Usher et al to be almost 80% in 2012[4]

DKA is associated with increased risk of mortality: The object of our study was to describe the clinical presentation of T1DM and factors associated with DKA in children and adolescents aged 6

months and above, followed up at the Paediatric Hospital David Bernardino (HPDB) In Luanda, Angola.

MATERIALS AND METHODS

Study Site: This study was conducted at the Endocrine clinic of David Bernardino Hospital, which is a level three public hospital located in the capital city of Angola, Luanda. David Bernardino Paediatric is a teaching referral hospital, with an endocrine clinic functioning once a week and attended by 10 - 20 diabetic children per week

Study Design: The study was a hospital based cross-sectional study. Sample size was calculated using the Kish Leslie formula (1965) with an estimated prevalence of DKA among TIDM children of 9.5% as per Majid *et al* Giving a minimal sample size of 67.

Study population*:* This consisted of children aged 6 months of age and above, diagnosed with TIDM and on follow up at David Bernardino Paediatric hospital- Paediatric Endocrine Clinic. The recruited subjects had a questionnaire administered to patients/ caretakers until a sample size of 80 subjects was attained.

Data collection: Recruitment of participants was conducted at the Paediatric Endocrine weekly clinic from December 2021 to March 2022. All subjects meeting the inclusion criteria (inclusion criteria: diagnosis of T1DM, 6 months and above) and whose parents gave an informed consent (in fact, no parent refused to give an informed consent) to participate in the current study were selected on a consecutive basis to the number of 80 children. Selected subjects received a predesigned standard structured questionnaire which included information on the socio-demographic characteristics, clinical signs and symptoms as well as factors associated with DKA at diagnosis. This was followed by a clinical examination and a rigorous review of the child clinical file for additional information.

Data management and analysis: Data entry template was created using SPSS for data entry version 3.0. Data was checked for completeness and corrected at source. Data entry was done in duplicate for validation (double entry) and cross-checked for entry error and range checks. The data was cleaned and validated before analysis. Data Analysis was done using SPSS version 23. To ensure confidentiality all personal identifiers were left out of the data set**.** The characteristics of children was described using means and medians for continuous variables. Proportions was compared by Chi-square. Where violations of a chi square test were observed e.g. the expected numbers of observations per cell were less than 5, the fisher's exact test was used in estimating the P value. Continuous variables were tested for normality by Shapiro-Wilk test. Students' test and Mann-Whitney-U test were used for normally distributed and skewed variables, respectively. Finally, a multivariable analysis to identify predictor factors associated with DKA at diagnosis was conducted.

P – Value of ≤ 0.05 was considered significant.

Ethical considerations: Ethical clearance was sought and obtained from David Bernardino Paediatric Hospital, research department and from its ethical committee. A written consent was obtained from the caretakers/guardians who was willing to participate in the study. An assent was also sought from all children aged 8 and above.

RESULTS

During the study period (From December 2021 to March 2022), 80 caretakers/patients were interviewed. Of the 80 patients studied, 43 (53.5%) were female, age > 10 years 53(66.25) and had again more than 10 years at the time of T1DM diagnosis 38 (47.5%). Regarding origin, the majority of the study participants, were coming from municipality of Viana 24 (30%), followed by the municipalities of Luanda (25.0%), Talatona (11.25%), Cazenga (10.0%).

Table 2. Distribution of sociodemographic factors of caregivers

Characteristics	Number	Percentage (%)
CAREGIVER		
Father and Mother	57	71,25
Single Mother	15	18,75
Single Dad	2	2,5
Grandmother	2	2,5
Other caregiver	4	5,0
Level of Education		
No schooling	3	3,75
*Primary education	14	17,5
*First Cycle of secondary school	19	23,75
*Second cycle of secondary school	25	31,25
Higher education	19	23,75
MARITAL STATUS		
Single	13	16,25
Married	30	37,5
*Lives in a de facto union	31	38,75
Widower	5	6,25
Divorced	1	1,25
PROFESSION OF THE CAREGIVER		
Unemployed	3	3,75
self-employed	22	27,5
Civil servant	33	41,25
Private	8	10,0
Maid	14	17,5

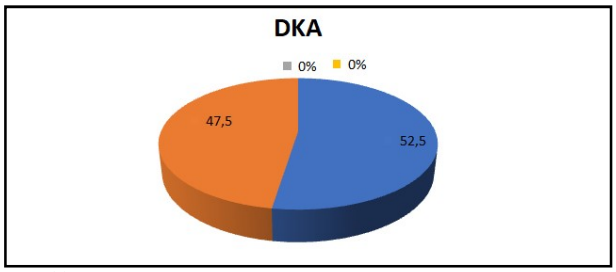
Source: Data collection form.
*Lives in a de facto union: not officially married but live as such for more than 3 years
*Primary education: from grade 1 to grade 6
*First Cycle of secondary school: from grade 7 to grade 9
*Second cycle of secondary school: from grade 10 to grade 13

Regarding the caregivers, the vast majority of the subjects were living with both the father and the mother 57(71.25%), while the majority of caregivers were living in a de facto union 31 (38.75%), had at least completed the second cycle of secondary school 25 (31.25%) and were civil servants 33 (41,25%) (Table no. 2).

Table 3. Clinical presentation in patients with T1DM

SYMPTOMS	Number (N)	Percentage (%)
Polyuria	78	97,5
Polydipsia	70	87,5
Weight Loss	66	82,5
Polyphagia	51	63,75
Nocturnal enuresis	22	27,5
Nausea/vomiting	27	33,75
Lethargy/drowsiness	31	38,75
Difficulty breathing	27	33,75
Coma/Alteration of consciousness	42	52,5
Ill-defined symptoms	66	82,5
DKA	42	52,5

Source: Data collection form.



Source: Table No. 3
52% of patients presented with DKA and 48% had no DKA at diagnosis

Chart 1. Distribution of patients who had DKA or not at the time of diagnosis

The classic signs of diabetes were the most frequent, with polyuria in 97.5%, polydipsia in 87.5% and weight loss in 82.5% of patients. While 42 (52,5%) of the participants had DKA at the time of diagnosis of T1DM (Table No. 3).

Among the sociodemographic factors studied, only age at diagnosis (p=0.035) was significantly associated with DKA, as subjects aged more than 10 years of age were more likely to present with DKA at the time of diagnosis. It was noted as well that the children of a caregivers who had only the first cycle of secondary school completed had an increased risk (p=0.068) of having DKA at the time of diagnosis compared to the children of caregivers with a completed second cycle secondary school (Table No 4)

Table 4. Bivariate logistic regression of patient characteristics associated with DKA

Characteristics	OR (95% CI)	p-value
SEX Male	1,00	
Female	0,53(0,24-1,44)	0,249
AGE GROUP		
< 3 years	1,00	
3 - 10 years	1,600 (0,137-18,723)	0,708
> 10 years	0,615(0,230-1,646)	0,333
PATIENT LEVEL OF EDUCATION		
No schooling	1,00	
Preschool	1,250 (0,164-9,538)	0,830
Primary education	0,313 (0,041-2,384)	0,262
First cycle of secondary school	0,542 (0,142-2,072)	0,370
Second cycle of secondary school	0,781 (0,202-3,016)	0,720
AGE RANGE OF DIAGNOSIS		
< 3 years	1,00	
3 - 10 years	0,542 (0,132-2,222)	0,395
> 10 years	0,352 (0,133-0,930)	0,035

Table 5. Bivariate logistic regression of caregiver's characteristics associated with DKA

Characteristics	OR (95% CI)	Valor p
CAREGIVER		
Father and mother	0,000	
Single mother	0,000 (0,000-)	0,999
Single father	0,000 (0,000-)	0,999
Grand parent	1,000 (0,000-)	1,000
Others	0,000 (0,000-)	0,999
Level of education of caretakers		
No schooling	1,00	
Primary education	4,333 (0,326-57,649)	0,267
First Cycle of secondar school	3,900 (0,906-16,789)	0,068
Second cycle of secondar school	2,979 (0,789-11,248)	0,107
Higher education	2,758 (0,791-9,613)	0,111
MARITAL STATUS		
Single	1,00	
Married	0,000 (0,000-)	0,689
Lives in a de facto union	0,000 (0,000-)	1,000
Widower	0,000 (0,000-)	1,000
Divorced	0,000 (0,000-)	1,000
PROFESSION OF THE CAREGIVER		
Unemployed	1,00	
Are self-employed	1211 (0,000-)	0,999
Civil servant	1,313 (0,334-5,162)	0,697
Private	0,553 (0,156-1,956)	0,358
Maid	0,450 (0,076-2,669)	0,379

Fonte: Formulário de recolha de dados.

None of the sociodemographic factors of the caregivers were associated with DKA as the first manifestation of T1DM, but children whose caregivers had only completed the first cycle of secondary school had higher risk of presenting DKA at the diagnosis of T1DM as compare to children whose parent has at least the second cycle of secondary school concluded at the time of the study (p=0,068). After successful iterations in multivariate modelling, the significant predictors for DKA at diagnosis in a patient seen at the endocrinology follow-up consultation were the absence of a family member with diabetes, specifically the absence of a diabetic aunt (p=0.035), and particularly no family member on insulin therapy (p=0.031).

There was also a statistical association between caregiver schooling and DKA at diagnosis, where children of caregivers with first cycle have a higher risk of presenting DKA at diagnosis when compared to children of caregivers with second cycle (p=0.058)

Table 6. Multivariate analysis of sociodemographic factors associated with DKA

C ffeatures	OR (95% CI)	P value
Age < 3 years	1,00	
3 - 10 years	7,685 (0,001-91191,900)	0,670
> 10 years	0,199 (0,004-9,713)	0,416
Diabetic mother No Yes	1,00 0,000 (0,000-)	1,000
Diabetic brother No Yes	00 0,000 (0,000-)	0,999
Diabetic sister No Yes	0,00 0000 (0,000-)	0,999
Diabetic aunt No Yes	1,00 591,845 (1,566-223725,964)	0,035
Diabetic uncle No Yes	0,00 4,848 (0,055-428,672)	0,490
Family member on insulin therapy No Yes	,00 0,001 (0,000-0,538)	0,031
Caregiver's education level		
No schooling	0,00	
Primary education	44,500 (0,188-10545,253)	0,174
First cycle of secondary school	20,747 (0,906-474,846)	0,058
Second cycle of secondary school	4,955 (0,336-73,038)	0,244
Higher education	1,508 (0,106-21,471)	0,762

Source: Data collection form.

DISCUSSION

T1DM is currently the most prevalent paediatric endocrinopathy and one of the most common chronic conditions in children and adolescents. This study was carried out with the main objective of describing the clinical presentation of T1DM and factors associated with DKA at presentation in children aged 6 months to 19 years followed in a national paediatric hospital in Angola. The results of the present study show a female predominance (53.75%) in children on follow up; similar results were reported in a study conducted in South-Eastern Nigeria[5] and a cross sectional study in Ghana by Emmanuel et al. who found a female prevalence of 71%[6]. But these findings were contrary to the results of other studies conducted in Saudi Arabia, which showed a male predominance of 52%[7], While Majaliwa *et al* have found an equal gender distribution among children in Africa [8]. Recently we started to understand the genetic aspect of T1DM, although there is still a large gap to be clarified. It is certainly an autoimmune disease, but a very strong female bias has never been demonstrated, explaining the different finding in terms of sexual dominance in different settings and different cohorts. The difference found in this study is not substantial enough and may be explained by our relatively small sample size. According to the age of the children participating in this study, most patients (66.25%) were older than 10 years and 30% were between 3 and 10 years old. This scenario was almost the same when it comes to age at diagnosis, as (47.5%) of the participants were over 10 years of age at the time of T1DM diagnosis (47.5%), while 42.5% were between 3 and 10 years old and only 10% of the children recruited in this study were under 3 years of age; similar findings were reported in two studies from Saudi Arabia that reported a first increased incidence of the diagnosis of T1DM between 6 - 7 years and a second increased incidence above 10 years of age, occurring mainly in girls [9,10]. This can be explained

by the fact that the clinical expression of T1DM is strongly influenced by other counter-regulatory hormones, such as growth hormone and sex hormones. This high number of patients presenting clinical expression of T1DM around puberty confirms the well-known theory that the incidence and clinical manifestation of T1DM are influenced by counter regulator hormones[11]. In terms of clinical presentation at the time of diagnosis, most of the patients in the present study had the classic triad of diabetes: polyuria, polydipsia, and weight loss. This was demonstrated long ago in a study conducted in Sudan by Elamin et al.,[3] and more recently by Al-*Yaarubi* et al in Oman - Saudi Arabia.s[7].

As stated by Nicholas Thomas, T1DM has a traditional presentation in children and commonly presents with as a triad of polyuria, polydipsia, and weight; what is different with the presentation in adults who have different presentations[12] The current study finds that 52.5% of the patients on follow-up in the endocrinology clinic of HPDB for T1DM had DKA at the time of diagnosis. This finding corroborates a study conducted in similar setting by Honesta K, where almost 40% of patients had DKA at the time of diagnosis [13]. Other studies from other developing countries have reported even higher rates of DKA at the time of T1DM diagnosis: South Africa (70%), Congo (90%), Benin (77%), and Ethiopia (80%)[14,15,16]. On the contrary, developed countries observed a low prevalence of DKA at the time of diagnosis of TDM1, such as Sweden (14%), and England (39.8%)[17,18]. This may be due to the high level of awareness among parents and primary care physicians, as well as good and accessible health services that culminate in an early diagnosis with reduced risk of DKA in high-income countries. However, some authors have raised the hypothesis of these variations in the worldwide incidence of DKA at presentation to be explained by genetic and/or environmental factors[11]. This hospital-based cross-sectional analytical study provides a comprehensive synthesis of factors associated with diabetic ketoacidosis at diagnosis in children and adolescents on follow up for T1DM at David Bernardino Paediatric Hospital (HPDB) in Luanda- Angola. In a bivariate analysis, it was found that age > 10 years at the time of diagnosis in children with T1DM was associated with higher risk of DKA. This contradicts the finding of a meta-analysis consisting of 32 studies, which found that children < 2 years of age were 3 times more likely to have DKA than children > 2 years of age [19]. But similar findings were described in a study by Hye et al in Korea [20] who found an increased likelihood of DKA at the time of diagnosis in children > 12 years of age and quite comparable to the finding of a study conducted at a tertiary centre in Pennsylvania in 2020, where age <3 years and > 9 years at diagnosis had a significant association with DKA at diagnosis [21].

This can be explained by the fact that the clinical expression and severity of T1DM is strongly influenced by other counter-regulatory hormones, such as growth hormone and sex hormones, which show a very particular, progressive increase starting between 8 and 10 years, depending on gender[22,23] After successful iterations at the multivariable modelling, the significant predictors for DKA at diagnosis of T1DM were: Absence of family member with diabetes, especially aunt with diabetes (p=0.035), no family member on insulin therapy (p=0.031), in multivariate analysis, the significant predictors for DKA at the time of diagnosis. Similar findings were observed in a systematic review that showed that having a family history of diabetes mellitus (DM) was associated with decreased risk of DKA at presentation [24]. The possible explanation for this relative protection of a family history of T1DM is most likely due to increased awareness and better recognition of signs and symptoms of hyperglycaemia among families with diabetes experience. It is also possible that a family history of T1DM, especially when using insulin therapy, alerts physicians to an increased possibility of diabetes mellitus in a child with some classic signs and symptoms of diabetes. Although no significant differences were identified between caregivers' schooling and DKA at the time of diagnosis, children of caregivers with a primary cycle have a higher risk of having DKA at the time of diagnosis when compared to children of caregivers with a second cycle (p=0.058). This finding is not uncommon, as a number of studies also show that children from families in which the parents had a higher education level have a reduced risk of DKA at the time of diagnosis[16,24]. The higher literacy rate is obviously associated with health awareness, and therefore you are likely to seek services at the health facility before severe symptoms.

CONCLUSION

The majority of our study subjects presented with the classical signs of diabetes at the diagnosis of T1DM: Polyuria in 97.5%, polydipsia in 87.5%, and weight loss in 82.5% of patients. More than half (52.5%) of the study subjects presented with DKA at the time of T1DM diagnosis. After successful iterations at the multivariable modelling, the significant predictors for DKA at diagnosis of T1DM were: Absence of family member with diabetes, especially aunt with diabetes (p=0.035), none family member on insulin therapy (p=0.031), and caregiver's level of education (p=0.058).

Recommendations: With a prevalence of 52.5% in diabetic children at diagnosis, DKA remains a serious and common problem in diabetic children seen at HPDB and deserves a well-coordinated multisectoral approach in the medical community and the general population. There is a need to increase public awareness campaigns and training about the early symptoms of T1DM to encourage early diagnosis. Special attention should be given to adolescents presenting classical signs of diabetes and to the family history of insulin-dependent diabetes. Improving the general population's level of education will contribute significantly not only to reducing severe events in diabetic children but also to reducing avoidable child deaths. We than recommend conducting a large-scale multicentre analytical study for a better understanding of the main predictors at the national level among Angolan population.

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Conflict of interest: We do not have any conflict of interest.

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