

CHARACTERISTICS AND ASSOCIATED FACTORS FOR TYPE 1 DIABETES MELLITUS AND DIABETIC KETOACIDOSIS AMONG YEMENI CHILDREN IN SANAA, YEMEN

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ABSTRACT

Introduction: Type 1 diabetes (T1DM) is a chronic debilitating disease affecting children with a serious fatal complication, diabetic ketoacidosis. Scanty literature is available about the epidemiological characteristics of (T1DM) among Yemeni children in Sanaa.

Methods: This is a retrospective descriptive study performed in the most important referral hospital and the National Diabetes Center in Sanaa. Data such as age, sex, residency, family history were collected by a pretested data collection form.

Results: Total enrolled patients were 163. Mean age at diagnosis was 10.1 years (± 3.6). Mean age among females was slightly lower than that of male (9.8 years, 10.2 years respectively). (61.3%) of patients were in the age group 10-14 years at the time of diagnosis. Some female predominance was noted with male to female ratio of 0.9. 66.9% of patients came from Urban areas, although relatively more DKA patients came from rural areas. Positive family history was detected only in 12 % of patients. The highest peak of T1DM was during winter, 62(38%).

Conclusions: Mean age at diagnosis of 10.1 years, mean age among females lower than male, slight female predominance, winter seasonality and urban residency were the most prominent epidemiological features among T1DM patients enrolled to this study. Moreover, polydipsia and polyuria were the hall mark clinical presentation which can be a target for health education for parents. Exclusive breast feeding was an important protective factor in this study, which is another target for health education.

KEYWORDS: T1DM, DKA, Pediatrics, Sanaa, Yemen, Characteristics

INTRODUCTION

Diabetes Mellitus is a chronic progressive disease characterized by constantly high blood glucose levels. (1) Type 1 diabetes mellitus, T1DM, (formerly known as insulin dependent) is caused by insulin deficiency where pancreas produces little or no insulin. It is treated by lifelong administration of insulin and it is currently not preventable. (2) It accounts for about 10% of all diabetes, affecting about 15 million in the world. (3)

The Middle East and North Africa (MENA) region is considered to have a lower incidence of childhood T1DM compared with Europe and North America (IDF, 2009) (4). Arab countries have the second highest incidence rates of type 1 DM globally, and it is expected that the incidence will increase by 96.2 % in 2035. Saudi Arabia, Kuwait and Qatar are the three countries with highest incidence rate (5).

Girls and boys are almost equally affected. The incidence increases with age and peaks at puberty.(6) Rural residence, positive family history of T1DM, early introduction to cow milk in the first year of age, stressful life events during pregnancy, maternal age less than 25 years and higher number of meals per day were considerable associated factors of T1DM. Moreover, breastfeeding, and early introduction of fruits as well as vitamin D supplementation has protective effects. (7, 8).

Diabetic ketoacidosis (DKA) is a frequent clinical presentation of children with new onset T1DM. It occurs as a presenting feature in 15-67 % of children with T1DM (9). This serious complication is associated with cerebral edema with significant morbidity and mortality (10). In a large study in Saudi Arabia, DKA was common among children and adolescents with T1DM, the study revealed that major risk factors were inability to keep a healthy lifestyle and ingestion of excessive amounts of sweets (11). Other risk factors included low socioeconomic status, higher HbA1c and African American race: lower serum C peptide, preceding infection, and delayed diagnosis (12, 13). Among the few studies in Yemen, one study revealed the incidence rate of T1DM to be 10.5 %. Female gender and positive family history were important risk factors (14). This study aims to describe the factors associated with the development of T1DM as well as those related to the development of DKA among Yemeni children.

Subjects and Methods

This was a cross sectional Hospital based study, performed in Sana'a city as it represents the largest accumulation of population in Yemen (2.006.619). The study was performed over two years from 1st of April 2011 to 30th April. Children with T1DM aged from 1 year up to 14 years seen in the National diabetic center (NDC), Pediatric ward, emergency room (PER) and intensive care unit (PICU) at Al-Thawrah Modern General Hospital were the target population. Sample size was 163, calculated using the statistical program Epi-infosoftware, version 7. A pretested structured questionnaire was used to collect demographic data and predisposing factors. It included a group of questions regarding sex, age, consanguinity and other factors. Direct interview with the mother/care giver were performed. Data were entered and analyzed using SPSS program version 21.0. Descriptive statistics, frequencies and Chi square tests at 5% significant levels were generated using the software.

Ethical consideration: Approval was obtained from the Ethical Committee, University of Sanaa. Verbal informed consent was taken from the parents/care giver before the interview. Confidentiality was assured and maintained. Children's names were replaced by numbers. Data was accessed by participating researchers only.

RESULTS

Table 1: Demographic Features of the Study Population (n=163)

Demographic features	Mean (\pm SD)	Range
Age at diagnosis (Yrs)	10.1 (\pm 3.6)	1-14yrs
Age at diagnosis in male (Yrs)	10.2 (\pm 3.8)	1-14yrs
Age at diagnosis in female (Yrs)	9.8 (\pm 3.4)	1-14yrs
Age (Yr) Groups at Diagnosis	No.	Percent (%)

• 1 - < 5 years	22	13.5%
• 5 - < 10 years	41	25.2%
• 10 - 14 years	100	61.3%
Gender		
• Male	80	49%
• Female	83	51%
Residence:		
• Urban	109	66.9%
• Rural	54	33.1%
Parents' consanguinity		
• Present	47	28.8%
• Absent	116	71.2%
Family history of T1DM		
• Absent	143	87.7
• Present	20	12.3%
1st degree	12	7.3%
• Sisters	7	4.3%
• Brothers	3	1.8%
• Fathers	2	1.2%
2nd degree	8	4.9%
• Uncles	5	3.1
• Aunts	3	1.8%
Season at diagnosis		
• Winter	62	38.0%
• Autumn	37	22.7%
• Spring	34	20.9%
• Summer	30	18.4%

Table (1) shows some demographic characteristics of the enrolled children in the study. The general mean age of enrolled children with T1DM was 10.1 (± 3.6) years. The mean age at diagnosis in males and females were 10.2 (± 3.8) and 9.8 (± 3.4) years respectively. A hundred patients, (61.3%), were in the age group 10-14 years at the time of diagnosis. Two peaks of age were detected, the first being between 10-14 years and the second was 5-<10 years. Females represented 83 (50.9%) of the cases and males represented 80 (49.1%) with male to female ratio of 0.9. The mean (\pm SD) duration of symptoms before presentation was 20.8 days (± 6.3). Most of the children included in the study were from urban areas, 109 (66.9%). Parents' consanguinity was found in 47(28.8%) cases and positive family history of T1DM was obtained in 20(12.3%) cases. First and second degree positive family history of T1DM was obtained in 12(7.3%) and 8(4.9%) cases respectively. Regarding the seasonality, the highest peak of T1DM was during winter, 62 (38%), followed by autumn and spring, 37 (22.7%) and 34 (20.9%) respectively. The lowest peak was during summer and is present in 30 (18.4%) cases.

Table 2: Type of Infant's Feeding and Time of Introduction of Artificial Milk among the Enrolled Children

Variables	No.	Percent%	p- value
Type of infant Feeding:			
• Exclusive Breast feeding	35	21.5%	0.000*
• Artificial milk feeding	128	78.5%	
Total	163	100%	
Type of infants feeding	Mean age at diagnosis (\pmSD)		
Exclusive Breast feeding (n=35)	12.7 \pm 1.8		0.000*

Artificial milk feeding (n=128)	6.6±3.7	
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*p value < 0.05 is considered statistically significant

Table (2) shows that children who received artificial feeding during the first six months of life were more likely to develop T1DM, 128 (78.5%), compared to those who received exclusive breastfeeding (21.5%) (p= 0.000). Time of the introduction of artificial feeding was not a significant factor in this study. Table (2) also shows that the mean age at diagnosis was significantly older among those who received exclusive breastfeeding 12.7 ±1.8 years, compared to those with artificial milk feeding, 6.6±3.7 years, (p=0.000).

In the majority of the enrolled children, (63%), no specific provoking factor was identified. Psychological trauma preceded the onset of T1DM in 28 (17.2%) and infection which occurred in 33 (20%) of cases. Mumps was the commonest infection preceded T1DM and present in 27% of cases followed by pharyngitis (18%), Figure 1.

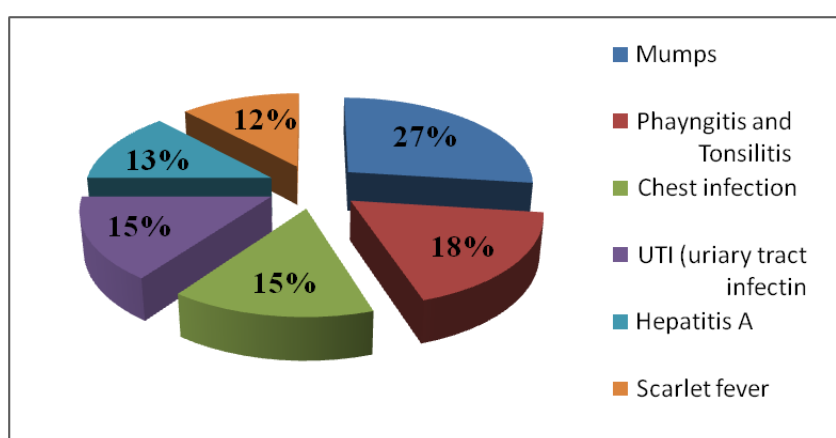


Figure 1: Infections preceding the diagnosis of T1DM.

At the time of diagnosis, Polyuria and polydipsia were observed in all patients presented with DKA and Non DKA, 95 (100%) and 68 (100%) respectively. Weight loss was present in 89 (64%) and 50 (36%) in DKA and Non- DKA cases respectively (p 0.001). Nocturnal enuresis was a main presenting feature among patients presented with DKA, 95 (70.4%), compared to Non DKA patients, 40 (29.6%) (p 0.000). On the other hand, polyphagia was more prominent among Non DKA patients, 38(52%), compared to DKA patients, 35(47.9%). Disturbed consciousness was an important presenting feature among DKA patients, 94 (88.7%), compared to Non DKA patients, 12(11.3%), p = 0.000. History of preceding infection was higher among DKA- presented patients, 22 (13.5%), compared to Non DKA presented patients, 11 (6.7%), p=0.02. History of preceding psychological trauma was also more prominent among Patients presented with DKA, 20 (71.4%), compared to patients presented with Non DKA manifestations, 8 (28.6%), p=0.01, Table 3.

Table 3: Clinical Features of Enrolled Patients according to the Mode of Presentation (DKA and Non DKA)

Variable	DKA (n=95)	Non DKA (n=68)	p-value
Signs and symptoms at diagnosis			
• Polyuria	95 (100%)	68 (100%)	0.1
• Polydipsia	95 (100%)	68 (100%)	0.1
• Wt loss	89 (64%)	50 (36%)	0.001*
• Nocturnal enuresis	95 (70.4%)	40 (29.6%)	0.000*

• Polyphagia	35 (47.9%)	38 (52%)	0.01*
Levels of Consciousness			
• Impaired Consciousness (n=106)	94 (88.7%)	12 (11.3%)	0.000*
• Alert(n=57)	1 (1.8%)	56 (98.2%)	0.000*
Degrees Of Dehydration			
• Severe dehydration(n=61)	61(100%)	0(0%)	0.000*
• Moderate dehydration(n=58)	33(56.9%)	25 (43.1%)	0.000*
• Mild dehydration(n=44)	1(2.3%)	43 (97.7%)	0.000*
Infection preceding the diagnosis of T1DM(n=33)	22 (13.5%)	11 (6.7%)	0.02*
Psychological Trauma preceding the diagnosis of T1DM (n=28)	20 (71.4%)	8 (28.6%)	0.01*

*p value < 0.05 is considered statistically significant

In the current study, 95 patients (58.28 %) were presented with DKA at the time of diagnosis. More than a half were in the age group 10-14 yrs. 19 out of 22, (86.4%) of patients in the age group 1-<5years presented with DKA, compared to 3(13.6%) of patients presented with Non DKA at this age group, which is a significant difference, (p=0.009). Although more females were presented with DKA, 52(62.7%) compared to males, 44(55%), this difference was not significant. DKA presentation was significantly more prominent among patients from rural areas, 45(83.3%), compared to those from urban areas, 50(45.9%), (p=0.000). Consanguinity and positive family history were not significant factors affecting the mode of presentation, Table 4.

Table 4: Demographic Characteristics of the Enrolled Patients According to the Mode of Presentation

Variables	DKA (n= 95)	Non DKA (n= 68)	p-value
Mean Age at diagnosis (years ±SD)[range]	9.2 ±3.7[1-14]	11.4 ±3[3-14]	0.000*
Mean Duration of T1DM symptoms (days ±SD) [range]	11 ± 7.4 [2-30]	33.9 ± 13 [15-60]	0.000*
Age groups at diagnosis			
• 1-<5yrs (n=22)	19(86.4%)	3(13.6%)	0.009*
• 5 - <10yrs (n=41)	25(61.0%)	16(39.0%)	0.05
• 10-14yrs (n=100)	51(51.0%)	49(49.0%)	0.1
Gender			
• Male (n=80)	44(55%)	36 (45%)	0.2
• Female (n=83)	52 (62.7%)	31 (37.3%)	0.2
Residence:			
• Urban(n=109)	50(45.9%)	59(54.1%)	0.000*
• Rural(n=54)	45(83.3%)	9(16.7%)	0.000*
Positive Parents' consanguinity (n=47)	29 (61.7%)	18 (38.3%)	0.5
Positive Family history of T1DM (n=20)	11 (55%)	9 (45%)	0.7

*p value < 0.05 is considered statistically significant

DISCUSSIONS

This study investigated the epidemiological and clinical features of 163 T1DM pediatric patients presented to the main Pediatric hospitals and the National center of DM in Sanaa, Yemen. In this study, the mean age at diagnosis was 10 years, which approximates that of a study in Azerbaijan among 104 children with T1DM (15); this is slightly lower than that of another study in Haifa among a total of 199 children with T1DM which found the mean age at diagnosis to be 12.9 years (16). The peak age at diagnosis in this study was 10-14 years. This coincides with Nagrato et al., who concluded a similar peak age group (17) and Ahmadov et al. who reported peak age of 10 years at diagnosis (15). This peak age coincides with the pre-pubertal hormonal changes which triggers the appearance of the disease. This pre-pubertal changes start earlier in girls which explains the difference in peak age between male and female (18).

A slight female preponderance was found in this study. This was also found by Nagrato et al., (17) and by El-ziny et al. in Egypt, who reported a significant female predominance (18) in contrast to a study in Baku, Azerbaijan which reported slight male gender predominance (15), while a review study in Hungary reported equal incidence of both sexes (6). Positive family history of T1DM was obtained in only 12.3% of patients in this study, this was nearly corresponding to a retrospective study on 146 patients, where 14.4 % of them have positive family history of T1DM (19).

In this study, infants who received artificial feeding were at risk of developing T1DM compared with those who were exclusively breast fed. This risk was higher if artificial milk was introduced earlier than 3months of age. An Egyptian case control study has concluded similar results, moreover, the same study concluded the protective effect of exclusive breastfeeding, this may be explained by the changes of the gut microflora (20, 21), which can reverse the epigenetic changes that triggers autoimmunity in patients at risk (7). In this study, the provoking factors that precede the diagnosis of T1DM were undetectable in 63% of the cases, although in the rest of the population a trigger could be detected. In 20% of patients, this trigger was infection (mainly Mumps). This coincides with many studies which concluded the role of viral infections in the etiopathogenesis and the clinical emergence of T1DM (21, 22, 23, 24), although a weak association was found with Mumps (25).

According to the International Society for Pediatrics and Adolescent Diabetes (ISPAD), Diabetic ketoacidosis (DKA) is the most common cause of death due to T1DM (26) In this study, around 58% of patients were presented with Diabetic ketoacidosis (DKA). This resembles the results of a large study in Iran in which around 67% of newly diagnosed patients during 15 years of study had presented with DKA at diagnosis (27). These high numbers of patients presented first with DKA may be explained by the misdiagnosis of the early symptoms of T1DM (28).

In this study, the major clinical findings of patients with T1DM (DKA and non DKA) were polyuria and polydipsia where almost all patients developed these two symptoms before diagnosis. This also was reported in a current study in Ethiopia (29) and another one in Santiago, Chile (30).

Loss of weight is a common presentation among patients with T1DM. In this study, weight loss among DKA patients was detected among 64% compared to only 36% of those presented with non-DKA presentation. This is similar to a study by the Diabetic Association in Pakistan among patients from two diabetic centers, which detected 79.5% of newly presented patients with T1DM were presented with loss of weight (31). In contrast, study in Santiago, Chile of 15 years duration and another study in Saudi Arabia in Al Baha diabetic center has reported less percentage of children with DKA has presented with loss of weight (30, 32).

Impaired consciousness is a serious presentation of children with DKA and it represents an important predictor of mortality. It is associated with hypotension, renal impairment and metabolic acidosis (33). In the current study, the majority of patients presented with DKA have impaired consciousness compared to non DKA presentation. This coincides with the study reported by Chhapola and colleagues in India where 81% of children with DKA were presented with impaired consciousness (34). On the other hand, another retrospective study in South Africa over two years reported a lower percentage of DKA patients were presented with altered sensorium although the mean age was higher than this study (35). This presentation may be explained by high levels of counter-regulatory hormones leads to ketogenesis and release of ketones although the definitive mechanism is not clear (36, 37).

Dehydration is a clinical hallmark of DKA (38, 39). In this study, moderate to severe dehydration was present in 73% of cases at presentation. In contrast to this study, another study in Australia found that only 48.6% of cases had moderate to severe dehydration at admission (40). Dehydration was more common in patients presented with DKA than in patients presented with Non DKA and this is in agreement with what have been reported by Rochmah et al., in 2015 in Indonesia.(41) and Prasad et al. in India (42).

In the current study, infections have preceded the onset of T1DM in 33 patients (20%). Moreover, infection occurred more among those presented with DKA than Non-DKA patients. A Taiwanese study has reported that DKA was preceded by febrile illness as a predisposing factor (43) and another study in Korea among seven centers, has reported acute infections among the predisposing factors of DKA (44). The link between glycemic control and infections is well established since hyperglycemia predisposes patients to infection, which in turn can deteriorates glycemic control and predisposes to DKA (45).

In the current study, psychological stress had preceded the onset of T1DM in 17% of cases, but significantly preceded DKA patients rather than Non DKA. In their review article, Wanger and colleagues reported an association between psychological stress and DKA, this may be due to decreased adherence to treatment during the periods of stress or conflict (46). Moreover, another review study in 2019 had suggested further research on psychological stress in order to target it in preventing DKA (47).

In this study, the mean age of children presented with DKA was significantly lower compared to those with Non DKA. This is in correlation with a retrospective study in 2018 among children in three diabetic centers, which reported younger age as an independent risk factor for DKA (48). Moreover, severe acidosis was detected more among younger children (49). In this study, the majority of children presented with DKA were in the age group less than 5 years compared to non DKA. The same was concluded by the studies of Chumięcki and his colleagues (49) and Choleau et al. (50), although another 2-year study in France reported the age is not an independent risk factor of severe DKA in comparison to Non DKA (51). In the current study, DKA was more prominent among female patients compared to Non DKA presented children. This is also reported by a retrospective study in Aga Khan Hospital in Pakistan (52). On the contrast, Choleau and his colleagues and Chumięcki et al. did not report female gender as a risk factor.^{49, 50}.

More DKA patients came from rural than urban areas in the current study, this is also reported by a study in Canada (53) which may be explained by lower access to health facilities among children in rural areas which can delay the early diagnosis. On the contrast, an epidemiological study in Poland did not report any difference in presentation among rural and urban residency (54).

CONCLUSIONS

Female predominance, pre-pubertal peak age at diagnosis, rural residency, winter seasonality and infections as preceding factors were most important epidemiological features. Polyuria and polydipsia, nocturnal enuresis and weight loss represented the hall mark clinical presentations of the patients. Moreover, these presentations were more common among DKA presented patients. Younger age was an independent risk factor for DKA presentation as well as female gender. The majority of patients were presented at diagnosis with DKA, which is the point that should be acted upon by the health authorities to improve education of parents regarding the main clinical presentation and risk factors of this fatal disease.

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Author Contributions

First author designed the study, second author had revised the study design and wrote the manuscript, and the third author prepared the statistical issues, interpretation, tables and results. All authors revised and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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