

Presentation of Children with Diabetic Ketoacidosis in a Tertiary Pediatric Emergency Department in Costa Rica

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Abstract

Background: Children with diabetic ketoacidosis (DKA) present frequently to the emergency department (ED). Most children recover when treated with insulin, intravenous fluids, and electrolyte replacement; however, infrequent complications, such as cerebral edema may occur. We describe the presentation in the ED of children with DKA in Costa Rica.

Methods: Retrospective case series of patients aged 1 month to 15 years presenting to a tertiary ED with DKA during a 5-year period. Univariate analysis was performed with Odds ratios (ORs) and 95% confidence intervals (CIs). Comparisons were made between the groups using logistic regression.

Results: 104 patients were identified. Mean age was 8.6 years (SD 3.8) and 64% were female. Median time from onset of symptoms to ED presentation was 15 days (IQR 3-22 days). Sixty of the patients were previously healthy. Precipitating factor was identified in 20(29%) and 24 (23%) were DM 1 with poor control. Most presented with progressive onset of symptoms (73%). Vomiting (54%), polydipsia (75%) and polyuria (72%) were the most frequent symptoms. On examination dry oral mucosa (80%), lethargy (27%) and abdominal pain (20%) were the most common signs. The degree of dehydration on arrival was mild in 19 (18%), moderate in 41 (39%) and severe in 29 (28%). Laboratory findings on arrival: mean pH 7.14 (SD 0.14); bicarbonate 8.2 (SD 3.68); PCO₂ 23.6 (SD 7.4); sodium 133.63 (SD 6.79) and potassium 4.72 (SD 0.83). 25 (24%) patients had severe DKA with a mean age of 8.25 (SD 3.7). 7 patients were treated for cerebral edema, 16 had hypoglycemia and hypokalemia (8 each) during management. At least one risk factor for cerebral edema was identified in 92 patients. No mortality was found.

Conclusion: DKA poses significant risks of morbidity and mortality. It must be suspected and treated with fluids, insulin infusion, and careful monitoring for better outcomes.

Keywords: Diabetes; Diabetic ketoacidosis; General pediatrics emergency

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Introduction

Diabetic ketoacidosis (DKA) is a condition that results from absolute or relative insulin deficiency and the effects of the counter regulatory hormones. This produces an accelerated catabolic state with hyperglycemia, hyperosmolarity, lipolysis and ketogenesis, causing ketonemia and metabolic acidosis [1]. If this is not addressed in time, fatal dehydration and severe metabolic acidosis will appear with possible complications and even death.

Type 1 diabetes (T1DM) is one of the common endocrine diseases in children. It is estimated that worldwide 65 000 children under 15 years old will develop the disease every year. There is also an increasing global incidence rate per year about 3% and between 10-70% of these diagnosed children will present with DKA [2]. In Latin America the information in regards to DKA is non-existing. It is not well defined why some of these children will present with ketoacidosis. It is associated with multiple factors like patient's age, a more aggressive form of diabetes, children from

some minority groups, a history of prior infection or difficulty in recognizing symptoms [3]. The cardinal symptoms of diabetes (polydipsia, polyuria and weight loss) are often not recognized by patients and their families. Many patients have been assessed by a health care professional in one or more occasions, in the days or weeks before their diagnosis [4].

Pediatric patients with DKA present frequently to the emergency department (ED). Most children recover when treated with insulin, intravenous fluids, and electrolyte replacement; however, infrequent complications, such as cerebral edema may occur. This complication occurs in 0, 3-3% of childhood DKA and can be fatal. Non-fatal cerebral edema often leads to neurologic sequelae. Risk factors include receiving more than 50 cc/kg of fluid in the first 4 hours of treatment, younger age, and lower pCO₂, high BUN at presentation and bicarbonate treatment [5,6]. This is the first Latin American report about pediatric DKA in the Emergency Department.

Our main objective was to determine the clinical characteristics and management of patients with DKA on presentation to the emergency department of a tertiary hospital in a developing country; specifically describe the major differences of the patients according to the severity of DKA in children.

Methods

Study design

This was a retrospective descriptive study of children with DKA at the Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera" in San José, Costa Rica (nation's population ~ 4.5 million inhabitants). This is the only tertiary referral and teaching pediatric center in the country, with ~ 350 beds and around 125 000 annual emergency department presentations.

Study population

We included all children from 1 month to 15 years of age who had a hospital discharge diagnosis of diabetic ketoacidosis, and were admitted from January 1st, 2008 to May 31th, 2013. Patients who had incomplete data on their clinical charts were removed from the current analysis. Identification of diabetic ketoacidosis cases was based on discharge diagnosis using the Classification of Diseases 10th revision (ICD-10) codes.

Case definition

We define DKA as hyperglycemia (blood glucose > 11 mmol/L [\approx 200 mg/dL]), venous pH < 7.3 or bicarbonate < 15 mmol/L and ketonemia / ketonuria [1]. Mild DKA was defined as venous pH 7.3-7.2 or bicarbonate 15-10 mmol/L, moderate DKA as venous pH 7.2-7.1 or bicarbonate 9 - 5 mmol/L and severe DKA as venous pH < 7.1 or bicarbonate < 5 mmol/L.

Time from onset of symptoms to presentation was defined as time when the parents or caregiver detected that the patient had symptoms to the presentation of the patient to the ED. Mild and moderate DKA were combined for the purpose of the analysis.

Patient management protocol

Volume and potassium replacement: Volume deficit was replaced with isotonic solutions. During rehydration therapy

potassium concentration in the isotonic solution was of 40 mEq/L.

Insulin and dextrose: Insulin was administered by continuous infusion initially at a rate of 0.1 U/kg/h. As soon as the glycaemia was 250 mg/dL, a 5% dextrose solution was added to the therapy. Thereafter, strength of dextrose administration was changed according to the needs of the patient.

Sampling for blood gases and electrolytes was performed in venous blood after venous puncture following a standardized protocol.

Data collection

A standard data collection form was used to obtain information from clinical charts. The tool was completed following a review of the medical charts. Data was abstracted from electronic ED records by ED and endocrinology staff, admission and progress notes as well as laboratory and radiology reports. Data collected included demographics; age, past medical history, risk factors for DKA, timing of onset of symptoms, presenting symptoms and signs of DKA, imaging, investigations, interventions and complications. Presenting signs and symptoms were extracted according to the first ED notes.

Statistical analysis

Statistical analyses were performed using Epi info 3.4.1 (CDC-2007) and Stata 12 (StataCorp, College Station, TX). Presenting symptoms and signs of diabetic ketoacidosis were analyzed descriptively. Analyses were performed on the total number of episodes and presented as percentages with corresponding 95% confidence intervals. Continuous variables were presented as mean and SD (normal distribution) or median and inter-quartile range (IQR) (non-normal distribution). We made comparisons between the groups using logistic regression for binary outcomes. Results were presented as differences between proportions and odds ratios (ORs) for binary outcomes and mean differences for continuous outcomes. A step-wise multivariate logistic regression analysis was done for each outcome of interest.

Ethics

The study was approved by the hospital Institutional Review Board and ethics committee, Permission was obtained to review clinical charts and to ensure confidentiality patients were identified using their initials and ID hospital number only.

Results

A total of 122 patients were identified with the diagnosis of DKA. Of those, 18 patients were excluded from the analysis because of an initial pH > 7.35, HCO₃ > 15 or incomplete data from medical records. Patients ranged in age from 4.5 months to 15.6 years with a mean age of 8.6 years (SD 3.78). Twenty-two patients were less than 5 years old. The majority of patients were female (64.4%; 95% IC 55% to 73%). The average hospital stay was 7.8 days (SD 4.34); for mild DKA 7.8 days (SD 4.1), moderate DKA 7.2 days (SD 3.3) and severe DKA 9.2 days (SD 5.9). The median time from onset of symptoms to the diagnosis was 8.5 days (IQR 3 to 22 days). The demographic characteristics of children with DKA divided by severity is shown in **Table 1**.

Table 1 Demographics characteristics of children with DKA.

	Total N=104	Mild DKA N=29	Moderate DKA N=50	Severe DKA N=25	p-value
Age in years, Mean (SD)	8.6 (3.78)	9 (4.1)	8,52 (3.6)	8.25 (3.7)	-
Female Sex n (%)	67 (64.4)	16 (55)	37 (74)	14 (56)	-
Hospital stay, Days (SD)	7.8 (4.3)	7.8 (4.1)	7.22 (3.3)	9.2 (5.9)	0.14
Median Time of onset of symptoms, Days (SD)	15.4 (21.1)	21 (31.7)	12.3 (13.4)	15.4 (18.3)	0.27
Interhospital transfer n (%)	49 (50)	13 (46)	24 (51)	12 (50)	-

Thirty-eight percent of patients were known to have a pertinent past medical history (95%CI 29% to 48%) and 23% (95% CI 15% to 32%) have T1DM already diagnosed in the past. Most of the patients had a previous consultation before diagnosis (71%; 95%CI 62% to 80%). Forty five percent had one previous consultation (95%CI 34% to 56%), 39% (95% CI 29% to 50%) had two previous consultations, 8% (95%CI 2% to 14%) three previous consultations, 4% (95%CI 0% to 9%) four and 1.2% (95%CI 0% to 3%) 6 previous consultations before diagnosis.

Precipitating factors were reported in 20 patients (29%; 95%CI 18% to 40%). The most common precipitating factor was upper respiratory tract infections in 24% (95%CI 15% to 32%) of the patients. In regards to diabetes control for the patients known T1DM, poor metabolic control was reported in 15 patients (14.5%; 95%CI 7% to 21%) with 10 (58%; 95%CI 32% to 85%) of the patients missing at least 2 appointments in the last year. The median value of HbA1c for the T1DM patients was 9.15 (SD 1.8).

The main presenting complains according to frequency are shown in **Table 2**. The most frequent were: polydipsia (75%; 95%CI 66% to 83%), polyuria (72%; 95%CI 63% to 80%), vomiting (54%; 95%CI 44% to 63%) and respiratory distress (24%; 95%CI 15% to 32%). On physical examination the most common findings were dry oral mucosa (80%; 95%CI 72% to 87%), lethargy (27%; 95%CI 18% to 35%), toxic appearance (20%; 95%CI 12% to 28%) and abdominal pain (20%; 95% CI 12% to 28%). Weight loss was confirmed in 26 patients of 32 that had the pre DKA weight. Presenting symptoms and signs are summarizing in **Table 2** divided in two groups, mild/moderate DKA and severe DKA.

On admission patients were taken initial biochemical investigations as per protocol. Mean venous pH was 7.15 (SD 0.14), HCO₃ 7.5 (SD 3.6) and PCO₂ of 24 (SD 7.1). The median serum levels of Na, urea nitrogen, creatinine, and magnesium were in a range that did not need replacement during the treatment, 2 patients (2%; 95%CI 0% to 4%) associated serum phosphate <1 mmol/L and needed replacement.

Fluid replacement was based on clinical assessment of the deficit. Initially, patients received a bolus of normal saline with a mean volume of 20 ml/kg (SD 12.7) during the first hour of treatment. All patients received insulin as per protocol. Adjunctive bicarbonate therapy was administered by treating physicians in 6 (5.7%) patients, due to pH level less than 7.0. Sixty-two patients resolved the DKA at 12 hours of treatment and by 24 hours 80% of the patients. All patients with mild DKA, 80% of patients with moderate DKA and 68% of patients with severe DKA resolved by 24 hours.

Neuroimaging was requested in 6 patients (6%; 95%CI 1% to 10%) and were described as normal; 4 patients needed inotropic support (3.9%; 95%CI 0% to 7%) and 10 patients assisted

mechanical ventilation (9.7%; 95%CI 3% to 15%).

Ninety-two patients (92%; 95%CI 86% to 97%) had positive risk factors for cerebral edema. Seven patients (7%; 95%CI 2% to 12%) received treatment for cerebral edema but none meet the diagnostic criteria. The main risk factors present were hypocapnia at presentation after adjusting for degree of acidosis (78%), severe acidosis at presentation (18.4%) and greater volumes of fluid given in the first 4 hours (5%). Twenty-three patients (23%; 95%CI 14% to 31%) had asymptomatic hypokalemia during management, 8 patients (8%; 95%CI % to 13%) had hypoglycemia, 5 patients (5%; 95%CI 0% to 9%) were treated for shock and 2 patients (2%; 95%CI 0% to 4%) had deep venous thrombosis associated to central venous catheter. There were no deaths or "near death" episodes (**Table 3**).

Only 8 patients (8%; 95%CI % to 13%) were admitted to ICU (2 with severe DKA and 6 with moderate DKA). The ED medical staff managed the rest of the patients until DKA was resolved. Thereafter, patients were transfer from ED to the endocrinology ward.

Four variables were identified for inclusion in the step-wise multivariate logistic regression analysis for each outcome of interest. Each variable was associated with Severe DKA in the univariate analysis. Abdominal pain (p: 0.0017), respiratory distress (p: 0,012), altered state of consciousness (p: 0.038) and neuroimaging (p: 0. 027) were associated to severe DKA (**Table 4**).

Discussion

Diabetic ketoacidosis is a life threatening condition, commonly missed at the initial consult. As shown in our study, 71% had a previous consultation before the diagnosis was made, higher than other series [4]. This delay leads to children presenting with different severity of DKA.

In our study, 85% of newly diagnosed type I diabetes presented with DKA, which is higher than reported elsewhere [2,7,8]. Fifty patients presented with moderate DKA, however, this did not reach statistical significance. It is well established that the younger the age, the higher the risk of DKA as initial presentation of diabetes mellitus [8]. The mean age in our study was 8.6 years, and the majority of patients were more than 5 years old; this differ from the literature were the majority of patients with DKA were younger [1,9-12].

The median time from onset of symptoms to diagnosis was 8.5 days, however in mild DKA was as late as 21 days, which brings up the concern that referring physicians are not recognizing the classical symptoms of diabetes.

In our study the most common presenting symptoms were polyuria, polydipsia, vomiting, abdominal pain and respiratory

	Total N: 104			Mild/Moderate N: 79			Severe DKA N: 25			OR	95% CI	P value
	n	%	95% CI	n	%	95% CI	n	%	95% CI			
	Presenting Complain											
Abdominal Pain	44	42	32-52	28	35	24-46	16	64	43-84	0.3	0.1-0.86	0.01
Vomiting	56	53.8	44-63	39	49	38-60	17	68	48-87	0.45	0.15-1.2	0.1
Polyuria	75	72	63-80	56	71	60-81	19	76	58-94	0.76	0.22-2.34	0.61
Polydipsia	78	75	66-83	58	73	63-83	20	80	63-96	0.69	0.18-2.23	0.5
Polyphagia	12	11.5	5-17	8	10	3-17	4	16	0-31	0.59	0.14-2.97	0.42
Respiratory Distress	25	24.2	15-32	13	17	8-25	12	48	27-69	0.21	0.07-0.64	0.001
Physical Examination												
Kussmaul Breathing	31	29.8	20-38	18	23	13-32	13	52	31-73	0.27	0.09-0.78	0.005
Dry oral mucosa	83	79.8	72-87	62	78	69-87	21	84	68-99	0.69	0.15-2.4	0.54
Toxic appearance	21	20	12-28	13	16	8-24	8	32	12-51	0.41	0.13-1.37	0.09
Lethargy	28	26.9	18-35	19	24	14-33	9	36	15-56	0.56	0.19-1.7	0.24
Altered conscious state	18	17	10-27	9	11	4-18	9	36	15-56	0.22	0.06-0.77	0.004
Abdominal Pain	21	20	12-28	14	18	9-26	7	28	9-47	0.55	0.17-1.88	0.26
Severe dehydration	29	27.8	19-36	19	24	14-33	10	40	19-60	0.47	0.16-1.40	0.12

Table 2 Univariate Analysis of Clinical Features of DKA according to Severity of DKA.

Management	Total N: 104			Mild/Moderate N: 79			Severe DKA N: 25			OR	95% CI	P value
	n	%	95% CI	n	%	95%CI	n	%	95% CI			
Brain CT scan	6	5.9	1-10	2	3	0-6	4	17	0-32	0.13	0.01-1	0.011
Inotropic support	4	3.9	0-7	3	4	0-8	1	4	0-12	0.94	0.07-51	0.96
Mechanical Ventilation	10	9.7	3-15	8	10	3-17	2	8	0-19	1.29	0.23-13	0.75
CVC	13	12.6	6-19	12	15	7-23	1	4	0-12	4.2	0.57-19	0.14
Complications												
Cerebral edema	7	7	2-12	5	7	0-12	2	8	0-19	0.77	0.11-8.7	0.77
Positive Risk factors for Cerebral Edema	92	92	86-97	69	92	85-98	23	92	80-100	0.6	0.05-3.1	0.52

Table 3 Interventions of patients with DKA.

	Coefficient	p-value	OR	95% CI
Abdominal Pain	1,96	0,0017	7,13	2,09-24,3
Respiratory Distress	1,52	0,012	4,61	1,39-15,28
Altered Conscious State	1,34	0,038	3,82	1,07-13,62
Brain CT scan	2,19	0,027	8,95	1,28-62,56

Table 4 Multivariate Logistic Regression Step-wise.

distress. Patients with severe DKA were more likely to show all these symptoms, however only abdominal pain (OR 7.13; p=0.0017) and respiratory distress (OR 4.61; p=0.012) were statistically significant [13,14]. In severe DKA these symptoms are expected, because of greater degree of metabolic acidosis; therefore, Kussmaul breathing is more evident as a compensatory mechanism. Abdominal pain is explained because of more severe dehydration and electrolyte imbalance, causing muscular pains and cramping [8].

On physical examination the patients who presented with severe DKA, were more likely to present an altered conscious state compared to mild/moderate DKA (OR 3.82; p= 0.038); therefore these patients underwent more frequently to brain CT scan (OR 8.95; p= 0.027). Despite all scans performed being described as normal, 7% of the patients were treated for cerebral edema due to clinical suspicion and none meet the criteria [12,15,16]. Clinically apparent cerebral edema occurs in only 0.5% to 1% of

DKA episodes; however, cerebral edema that is asymptomatic or associated with only minor mental status alterations occurs much more frequently [6]. As this is a retrospective review we rely on data consigned on clinical charts, therefore we did not find other signs apart from altered mental status, as the reason why these 7% of patients were treated for cerebral edema. Many children have normal brain imaging at the onset of clinical cerebral edema and do not develop radiographic signs of edema until hours or days later [17]. The early treatment in these patients is critical in preventing neurological deterioration and the bedside evaluation should be very important in determine which patients will need treatment.

The prevalence of ketoacidosis in patients known type I DM was 23%, which is consistent with what has been reported in other latitudes. The most common precipitating factor in this group was lack of adequate control. Among these patients, 58% had missed at

least two appointments in the last year, which brings up concerns about adherence, dietary and nutritional recommendations, insulin titration and co-morbidities. In addition, social and psychological supports to keep them motivated and prevent bad outcomes and complications [1,7,8]. Even though it was not the aim of this study to review why diabetic patients missed appointments, we consider it as an important aspect that could lead to DKA, since these patients might be in risk specially if there was no close follows up of the diabetes management.

Ideally, this study would have prospectively identified and analyzed all patients presenting to the ED with hyperglycemia and acidosis to determine the relevance of the presence or absence of signs and symptoms in determining the likelihood of DKA and the severity. The current study is also limited by the retrospective extraction of data from the charts, which may lead to erroneous measures of the frequency of signs and symptoms. Our sample is small compared with other series, and we analyzed information from a single center. However, this is the only pediatric tertiary referral hospital in the country and it is likely that most patients with ketoacidosis were diagnosed and treated in our center.

Conclusion

Diabetic ketoacidosis is still a quite common problem in children with new onset diabetes, raising an opportunity to improve care for this population, looking into strategies to decrease its incidence at diagnosis. These strategies should involve both public and private health sectors, since all children with newly diagnosed DM in Costa Rica, are seen at our National Children's Hospital. The cost of caring for these children is considerably elevated, since the mean hospital stay is 7.8 days. On children with established type 1 DM, great efforts have to be made to decrease the possibility for them to present with DKA to the emergency department, the strategies should be focused on keeping families and children committed to a good metabolic control.

Credits to Paper

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