Evaluation of Clinical Differences of Newly Diagnosed and Formerly Diagnosed Pediatric Diabetic Ketoacidosis Patients

Eski ve Yeni Tanı Pediatrik Diyabetik Ketoasidoz Hastalarının Klinik Farklılıkların Değerlendirilmesi

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ABSTRACT

Objective: Our aim is to determine the severity, clinical features, presence of complications and outcome differences in previously diagnosed and newly diagnosed Type 1 Diabetes Mellitus (T1DM) patients followed up with diabetic ketoacidosis (DKA) in the pediatric intensive care unit.

Material and Methods: This study was conducted retrospectively in a 32-bed tertiary pediatric intensive care unit. The patients were divided into newly diagnosed and previously diagnosed T1DM. All collected data were compared between groups.

Results: 107 patients were included into the study. Most of the patients were male (51.4%). Most of the newly diagnosed patients were in the 6-10 age group (49.2%). When patient complaints were evaluated before admission, the complaint of nausea was statistically higher in previously diagnosed DM patients (p=0.041). The complaints of fatigue, polyuria, polydipsia, and weight loss were statistically higher in newly diagnosed Type-1 DM (p value 0.001, 0.001, 0.001, 0.001, respectively). Hypokalemia was statistically higher in the newly diagnosed DM group during diabetic ketoacidosis treatment (p=0.015). Although there was no difference between intensive care durations, total hospitalization days were statistically longer in newly diagnosed DM patients (p values 0.145, 0.007, respectively). All patients survived.

Conclusion: The school age group was the most common age group in newly diagnosed T1DM. While polyuria, polydipsia and weight loss are common in newly diagnosed Diabetic Ketoacidosis patients; Vomiting was common in diabetic ketoacidosis patients with previous diagnosis. Trainings, national advertisements, etc. should be done to increase the knowledge level of patients and families about these symptoms and the disease.

Key Words: Children, Diabetic Ketoacidosis, Intensive Care

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ÖZ

Amaç: Amacımız, çocuk yoğun bakım ünitesinde diyabetik ketoasidoz (DKA) ile takip edilen daha önce tanı almış ve yeni tanı almış Tip 1 Diabetes Mellitus (T1DM) hastalarının şiddeti, klinik özellikleri, komplikasyon varlığı ve sonuç farklılıklarını belirlemektir.

Gereç ve Yöntemler: Bu çalışma, 32 yataklı üçüncü basamak çocuk yoğun bakım ünitesinde geriye dönük olarak yapıldı. Hastalar yeni tanı almış ve önceden tanı almış T1DM olarak ayrıldı. Toplanan tüm veriler gruplar arasında karşılaştırıldı.

Bulgular: 107 hasta çalışmaya dahil edildi. Hastaların çoğu erkekti (%51.4). Yeni tanı alan hastaların çoğu 6-10 yaş grubundaydı (%49.2). Başvuru öncesi hasta şikâyetleri değerlendirildiğinde kusma şikayeti, daha önce tanı almış DM hastalarında istatistiksel olarak anlamlı derecede yüksekti (p=0.041). Yeni tanı alan Tip-1 DM'de halsizlik, poliüri, polidipsi, kilo kaybı şikâyetleri istatistiksel olarak anlamlı derecede yüksekti (p değeri sırasıyla 0.001, 0.001, 0.001, 0.001). Diyabetik ketoasidoz tedavisi sırasında yeni tanı almış DM grubunda hipokalemi istatistiksel olarak daha yüksekti (p=0.015). Yoğun bakım süreleri arasında fark olmamasına rağmen yeni tanı konmuş DM hastalarında toplam yatış günleri istatistiksel olarak daha uzundu (p değerleri sırasıyla 0.145, 0.007). Hastalarda mortalite görülmedi.

Sonuç: Okul yaş grubu, yeni tanı konan T1DM'de en sık görülen yaş grubuydu. Yeni tanı Diyabetik Ketoasidoz hastalarında poliüri, polidipsi, kilo kaybı sık iken; eski tanılı diyabetik ketoasidoz hastalarında kusma yaygın olarak saptandı. Hastalar ve ailelerin bu semptomlar ve hastalık hakkında bilgi düzeyini artırıcı eğitimler, ulusal reklamlar vb uygulamalar yapılmalıdır.

Anahtar Sözcükler: Çocuk, Diyabetik Ketoasidoz, Yoğun Bakım

INTRODUCTION

Diabetic Ketoacidosis (DKA) is one of the major reasons of hospitalizations into pediatric intensive care (1). DKA is a life-treating complication of Type 1 Diabetes Mellitus (T1DM) (2). DKA has several complications like hyponatremia, hypokalemia and hypoglycemia. DKA is also cause activation of inflammatory pathways, disruption of coagulation cascade and increase the risk for thrombosis and stroke (3). Cerebral edema is most important and fatal complication of DKA (4). Incidence of cerebral edema was 0.5-0.9%, but associated with mortality (4). Like incidence of T1DM, mortality rate of DKA vary between countries. In developing countries DKA-related mortality rate ranges from 6%-24% (4). In developed countries mortality rate was 0.15%-0.30% (4).

Presence of family history, geographic location, age and socioecomic status affects DKA progression in T1DM patients (2). DKA was more common in at the time of T1DM diagnosis in newly diagnosed T1DM (2). Formerly diagnosed T1DM patients are less suffers from DKA (2). Insulin negligence, insulin pump failure, or insufficient insulin dose affects DKA progression in formerly type T1DM (2).

Aim of our study was to identify severity, clinical characteristics, complication presence and outcomes differences of formerly diagnosed and newly diagnosed T1DM patients presented as DKA followed-up in pediatric intensive care unit. We also evaluate interventions before and during admission of patients.

MATERIAL and METHODS

Our study was conducted in a 32 bed third-level pediatric intensive care unit retrospectively. Study period was planned as 24 months dates between 01-August-2019/31-August-2021. All patients between one month old eighteen years were included into study followed as diabetic ketoacidosis. First admission was recorded in recurrent admissions of DKA. Patients without acidosis but had hyperglycemia or diabetic ketosis was excluded.

Diabetic ketoacidosis was diagnosed according to criteria of International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 guideline: 1)Serum glucose >200 mg/dl, 2) Venous pH<7.30, 3)Ketonemia or ketonuria presence (5).

Diabetic ketoasidosis severity was classified according to venous pH level as <7.30 mild DKA, <7.20 moderate DKA, <7.10 severe DKA (5).

Demographic data, presence of co-morbidity, presence of family history with DM variables were collected.

Duration of complaints, symptoms (fever, nausea, vomiting, diarrhea, malaise, tachypnea, polyuria, polydipsia, polyphagia and weight loss), interventions before Pediatric Intensive Care Unit (PICU) and family history were pre-intensive care variables.

In intensive care follow-up Glasgow Coma Score (GCS) at admission, DKA severity, laboratory parameters (blood count, electrolytes, corrected sodium level, blood gas parameters, liver functions tests, kidney function tests, serum glucose level, blood ketone), respiratory support therapies, complications during DKA treatment (hyponatremia, hypokalemia, hypophosphatemia, hypoglycemia, brain edema) was recorded.

Hypoglycemia was defined as serum glucose <60 mg/dl, hypokalemia as <3.5 mEq/L, hypophosphatemia as <4.6 mg/dl, hyponatremia as corrected serum sodium level <135 mEq/L. Corrected sodium (meq/L) was calculated as measured sodium+1.6x [serum glucose-100/100], effective osmolarity (mOsm/kg) was calculated as [2x plasma sodium]+ [serum glucose/18]. Outcomes were evaluated as intensive care duration in days, hospital duration in days and survival.

All patients were categorized as newly diagnosed Diabetes Mellitus (DM) and formerly diagnosed DM patients. Data collected from patients was compared between two groups. We took study permission by local ethic committee of Ankara City Hospital (E2-21-659).

Descriptive analysis of the results conducted by using the SPSS 17.0 software package for Windows (IBM Company, New York, NY). Categorical data expressed as proportions (%). Median and inter quartile range (25^{th}-75^{th} percentile) were used for quantitative data. Differences were evaluated by Chi-Squared test in cases of categorical variables; nonparametric test (Mann-Whitney U) for continuous variables. Data was considered statistically significant at $p < 0.05$.

RESULTS

During study period 115 patients were followed up in pediatric intensive care unit as DM. Eight patients were excluded because of diabetic ketosis. 11 patients had multiple admissions. First admissions of patients who had multiple admissions were collected. 107 patients were included into study. Demographic data was demonstrated in Table I. Most of the patients were male (51.4%). Adolescent age group were the largest group between our patients (57.0%). Most of the newly diagnosed patients were in 6-10 age groups (49.2%). Difference between age groups were statistically significant (p=0.001). Severity of DKA was not differ between age groups (p=0.637). There were not any differences between groups in pre-PICU interventions. If complaints before admission evaluated, nausea was statistically significant higher in formerly diagnosed DM patients (p=0.041). Malaise, polyuria, polydipsia, weight loss complaints were statistically significant higher in new diagnosed-Type-1 DM (p value respectively 0.001, 0.001, 0.001, 0.001). Time period between starting of symptoms till hospital admission was significantly longer in new diagnosed DM patients (p=0.001). Median time for disease duration in formerly diagnosed DM was 5 (2.0-7.25) years. Patients without family history of diabetes mellitus were suffered severe DKA more than patients with family history of diabetes mellitus (p=0.004).

Critical care follow-up and evaluation of complications were presented in Table II. Twelve patients GCS was below 15. Most of patients whose GCS <15 was between 6-10 years age (p=0.029). Below 5 year old age group distortion of conscious was seen at highest rate (30.0%). Impaired conscious did not differ in formerly or newly diagnosed DM patients (p=0.283). Medical treatments apart from regular insulin were oral antibiotic, proton pump inhibitors, hypertonic saline and sodium bicarbonate respectively. Invasive mechanical ventilation was applied to one patient for three days. Brain computerized tomography performed to two patients. Radiologic assessment of patients who had cranial screening did not show any sign

Table I: Demographic characteristics and pre-intensive care interventions of DKA patients.

Characteristics	DKA (Total) (n=107)	DKA (Formerly diagnosed) (n=42)	DKA (Newly diagnosed) (n=65)	p
Gender (Male), n (%)	55 (51.4)	22 (47.6)	33 (50.7)	0.871
Age (month), median (IQR)	126 (89-174)	161 (123-199)	109 (76-148)	0.352
Age groups, n (%)				0.001
0-5 years	10 (9.3)	2 (4.7)	8 (12.3)	
6-10 years	36 (33.6)	4 (9.5%)	32 (49.2)	
11-18 years	61 (57.0)	36 (85.7)	25 (38.4)	
Body weight (kg), median (IQR)	34 (22-50)	48 (31.5-57.0)	27 (20-41)	0.760
DM family history presence, n(%)	45 (42.1)	18 (42.9)	27 (41.5)	0.893
Pre-PICU interventions, n (%)				
Saline bolus	76 (71.0)	29 (69.0)	47 (72.3)	0.718
Hydration	39 (36.4)	17 (40.5)	22 (33.8)	0.489
Insulin treatment	30 (28.0)	15 (35.7)	15 (23.1)	0.157
Other treatments	12 (11.2)	2 (4.8)	10 (15.4)	0.091
Symptoms, n (%)				
Fever	11 (10.3)	6 (14.3)	5 (7.7)	0.275
Nausea	35 (32.7)	18 (42.9)	17 (26.2)	0.073
Vomiting	53 (49.5)	26 (61.9)	27 (41.5)	0.041
Diarrhea	5 (4.7)	4 (9.5)	1 (1.5)	0.057
Malaise	45 (42.1)	9 (21.4)	36 (55.6)	0.001
Tachypnea	17 (15.9)	7 (16.7)	10 (15.4)	0.860
Polyuria	46 (43.0)	2 (4.8)	44 (67.7)	0.001
Polydipsia	46 (43.0)	2 (4.8)	45 (69.2)	0.001
Polyphagia	4 (3.7)	0 (0)	4 (4.6)	0.103
Weight loses	36 (33.6)	1 (2.4)	35 (53.8)	0.001
Abdominal pain	22 (20.6)	10 (23.8)	12 (18.5)	0.506
Period before hospital admission (day), median (IQR)	3 (1-7)	1 (1-2)	7 (3-21.5)	0.001

DKA: *Diabetic Ketoacidosis,* ***DM:*** *Diabetes Mellitus,* ***IQR:*** *Interquartile Range,* ***PICU:*** *Pediatric Intensive Care Unit*

Table II: Evaluation of intensive care floow-up and complications of DKA patients.

	DKA (Total) (n=107)	DKA (Formerly diagnosed) (n=42)	DKA (Newly diagnosed) (n=65)	p
GCS at PICU admission, median (IQR)	15 (15-15)	15 (15-15)	15 (15-15)	0.233
DKA severity, n (%)				
Mild	45 (42.1)	19 (45.1)	26 (40.0)	0.780
Moderate	35 (32.7)	12 (28.6)	23 (35.4)	
Severe	27 (25.2)	11 (26.2)	16 (24.6)	
Venous blood gas parameters, median (IQR)				
pH	7.12 (7.05-7.22)	7.13 (7.06-7.21)	7.12 (7.03-7.22)	0.318
pCO2 (mmHg)	20.6 (15.9-24.7)	22.3 (18.6-26.1)	19.7 (15.6-23.5)	0.319
HCO3 (mmol/L)	6.8 (4.5-9.3)	7.9 (4.9-9.7)	6.4 (4.1-8.9)	0.668
BE (mmol/L)	-20.3 (-23.3- -16.5)	-19.1 (-22.6 --16.4)	-20.4 (-23.9- -16.4)	0.303
Lactate (mmol/L)	2.02 (1.52-2.91)	2.56 (1.67-3.66)	1.78 (1.48-2.51)	0.291
Biochemical parameters, median (IQR)				
Serum glucose (mg/dl)	437.0 (330.0-526.0)	459.5 (367.2-533.0)	500 (325.0-512.5)	0.564
Blood ketone level (mmol/L)	5.6 (4.6-6.1)	5.3 (4.1-6.0)	5.6 (4.9-6.1)	0.715
Sodium (mEq/L)	134.0 (131.0-137.0)	133.5 (130.0-137.2)	134.0 (131.0-137.0)	0.645
Potasium (mEq/L)	4.4 (4.0-5.1)	5.0 (4.4-5.4)	4.4 (3.8-4.4)	0.057
Phosphate (mEq/L)	4.1 (3.1-5.1)	4.9 (4.1-6.0)	3.5 (3.0-4.1)	0.042
Clor (mEq/L)	104 (100.0-108.0)	102.0 (97.5-106.2)	105.0 (101.5-109.0)	0.370
BUN (mg/dl)	28.0 (19.0-40.0)	39.5 (28.5-48.0)	21.0 (17.0-30.0)	0.106
Creatinine (mg/dl)	0.92 (0.76-1.11)	0.97 (0.85-1.18)	0.86 (0.71-1.04)	0.189
AST (U/L)	17 (12-25)	22 (12.7-28.2)	15.0 (11.0-21.0)	0.143
ALT (U/L)	18 (13-22)	20.0 (15.7-32.5)	16.0 (13.0-21.0)	0.605
Corrrected sodium (mmol/L), median (IQR)	142 (139.4-144.2)	141.9 (139.1-144.8)	142.0 (139.4-144.1)	0.506
Effective osmolarite (mOsm/kg), median (IQR)	291 (287.4-298.0)	291.1 (286.0-299.5)	291.0 (284.5-297.1)	0.390
Anion gap (mmol/L) median(IQR)	23 (20.5-27.0)	25.6 (20.5-29.0)	22.0 (20.4-24.3)	0.250
HbA1c (%), median (IQR)	11.9 (10.8-13.1)	11.3 (9.7-12.4)	12.1 (11.0-13.6)	0.487
DKA complications, n (%)				
Hiponatremi	6 (5.6)	3 (7.1)	3 (4.6)	0.579
Hipoglisemi	4 (3.7)	1 (2.4)	3 (4.6)	0.554
Hipokalemi	38 (35.5)	9 (21.4)	29 (44.6)	0.015
Hipofosfatemi	81 (75.7)	29 (69.0)	52 (80.0)	0.199
Brain edema	3 (2.8)	1 (2.4)	2 (3.1)	0.831
DKA resolution period (hour), median (IQR)	12 (8-18)	11.25 (7.0-15.0)	14 (10-19)	0.741

AST: *Aspartate amino transferase,* ***ALT:*** *Alanine amino transferase;* ***BE:*** *Base Excess,* ***BUN:*** *Blood Urea Nitrogen,* ***DKA:*** *Diabetic Ketoasidosis,* ***IQR:*** *Interquartile range,* ***GCS:*** *Glasgow Coma Scale,* ***PICU:*** *Pediatric Intensive Care Unit*

Table III: Outcomes of DKA patients.

	DKA (Total) (n=107)	DKA (Formerly diagnosed) (n=42)	DKA (Newly diagnosed) (n=65)	p
Intensive care period (day), median (IQR)	1 (1-2)	1 (1-1.25)	1 (1-2)	0.145
Hospitalization period (day), median (IQR)	10 (7-12)	8 (5-10)	10 (9-12)	0.007
Mortality, n (%)	0 (0)	0 (0)	0 (0)	

DKA: *Diabetic Ketoasidosis,* ***IQR:*** *Interquartile range*

of brain edema. Hypophosphatemia was the most common complication during treatment period. Hypokalemia was statistically higher in new diagnosed DM group during diabetic ketoacidosis treatment (p=0.015). Hypoglycemia was seen in 4 patients. Three patients with hypoglycemia were in severe DKA group (p=0.02). Brain edema was spotted in three patients. Hypertonic saline was applied to patients as brain edema treatment. Patients with brain edema cured without sequel.

Venous blood gas parameters, serum glucose and ketone levels of patients with low GCS and normal GCS presented in Table III. Patients with altered conscious had more severe acidosis, higher glucose levels but their ketone levels were lower.

Outcomes were presented in Table III. Although there was not any difference in intensive care days, total hospitalization days was statistically longer in newly diagnosed DM patients (p values

respectively 0.145, 0.007). Patients with low GCS had longer PICU hospitalization than patients with normal GCS (p=0.12). Hospitalization of these patients whose had low GCS a little bit longer than normal GCS patients but it was not statistically significant (p=0.051). All patients survived.

DISCUSSION

In our study, we spotted that new diagnosed DM was more commonly seen in school age children. Nausea was the most common symptom in formerly diagnosed T1DM patients, whereas malaise, poliuria, polydipsia and weight loss complaints were more common in new diagnosed DM patients. Time period between starting of symptoms till hospital admission time was longer in new diagnosed DM patients. Hypokalemia was higher in new diagnosed DM group during diabetic ketoacidosis treatment Total hospitalization days was longer in newly diagnosed DM patients group.

Incidence of diabetes mellitus is increasing in children and adolescents in the world and growing faster in particularly below 5 years age children (6). Annual increase of T1DM was 3% in children and 5% in adolescent age group (4). Children under 5 years old more often suffers from DKA (3). Apart from literature DKA was more common in adolescent age group in the previous study. Parental care difference may affect this result. Parents may be more careful about their children's behavior changes like polyuria, polydipsia etc. at small ages and early recognition of symptoms lead to reach early proper treatment An article about fifteen years experience of DKA patients also reported that DKA was more common in adolescent age group (7). In developed world most common admission in T1DM patients is hyperglycemia without acidosis. In developing and underdeveloped countries DKA is the most common type of admission of T1DM patients (8). The prevalence of DKA varies between countries (15-67%) (6). There are several risk factors related with DKA (9). Misdiagnosis at first visit, delay in treatment, previous infection history, younger age, low body mass index and low socioeconomic level were common risk factors (9). There should be more multi-center prospective studies to evaluate risk factors of DKA in Turkish children.

Polyuria, polydipsia and polyphagia which are starting symptoms of DM are ensued from hyperglycemia and glycosuria. If patients are not diagnosed at this stage, vomiting, abdominal pain, anorexia, dehydration, Kussmall breathing, loss of consciousness and finally coma will be seen in these patients (7). Most reported symptoms of the patient's with DKA were polyuria and polydipsia (10).

Most reported symptoms in newly diagnosed T1DM patients were polyuria, polydipsia and weight loss (7,10,11). Our study results also demonstrated same results with other studies in literature. Apart from literature, malaise and weight loss were common in our study group. Vomiting was also common in formerly diagnosed DKA patients like other studies (1,3).

A multicenter study from Europe was showed newly diagnosed DKA patients had symptoms at least two weeks (12). Articles from Turkey also reported that period before DKA diagnosis was usually two weeks (7,10,13). In our study, we reached our study populations admission time was same as other reports in literature. Formerly diagnosed DKA patients are more careful about DKA symptoms due to educations performed in their clinical care so their admission time was shorter than newly diagnosed T1DM patients.

Parent's unawareness of symptoms of DM may affect DKA incidence (14). Positive family history for T1DM is defined as a risk factor for DKA (15). We did not find any difference between formerly or newly diagnosed T1DM with positive family history of DM concurrently. But we found that severe DKA related with presence of DM family history. This result also suggests requirement of more public educations about awareness of DM. A public campaign about DM in Italy for health professionals and families lowered DM prevalence from 78 to 12.5% (6).

If we evaluate electrolyte disturbances of patients at admission and during treatment period, we found that hypophosphatemia was the most common electrolyte disturbance. This result did not show actual result because intravenous phosphate forms are mostly absent in our hospital so patients could not get IV phosphate support during treatment properly. Hypokalemia was the most common electrolyte disturbance in newly diagnosed DKA patients like other studies published from Turkey and other countries (1,4,7). Children with DKA usually suffers from hypokalemia because of transcellular potassium shift and increaring loss from the body because of vomitting and secondary hyperaldosteronism (5). A single center study from Turkey reported that hypokalemia was developed because of inadequate replacement (7). Hypophosphatemia could be seen in DKA patients result of osmotic diuresis and depletion of intracellular phosphate (5). Hypophospahatemia can cause several complications like rhabdomyolysis, respiratory failure, hemolysis, metabolic encephalopathy and myopathy (5). Pediatric DKA guideline did not recommend routine hypophosphatemia treatment but it recommends potassium replacement with potassium chloride and potassium phosphate together (5). Severe hypophosphatemia (serum phosphate levels <1 mg/dl) should be treated (5). Recent published single center study from Netherlands did not show any difference between hypophosphatemic and normophosphatemic adult DKA patients (16). There should be more studies done in pediatric DKA patients about electrolyte disturbances.

Brain edema was seen in DKA episodes in 1% of patients (7). Brain edema was the most serious complication of DKA (14). In our study group brain edema incidence (2.8%) was higher than literature data. This will be associated with our center was a

referral center in Ankara City and Central Anatolia region. More complicated cases referred to our facility. Despite that we did not see any mortality in our cohort.

There are several restrictions of our study. Our study was single-centered and retrospective. Parental education level and patients' socioeconomic conditions were not reported in patient files. Family history of diabetes did not classify as T1DM and T2DM result of invalid data. Severity of dehydration did not record at time of admission into patient files. The data of DM patients with old diagnosis whether DKA was present at the time of diagnosis could not be accessed because of missing registry. Treatments before PICU may not be recorded properly. Assessment of brain edema may be lacking and some patients with brain edema could not be detected. Nearly all DKA patients are hospitalized in PICU in our facility. But, there would be patients with DKA whom did not referred to PICU for follow-up and hospitalized to ward from emergency service. Our data will not show our countries proper DKA data. Multicenter prospective studies should be designed.

In conclusion, diabetic ketoacidosis is an important patient group in PICU. Most of the DKA patients were adolescent age group in formerly diagnosed T1DM patients. School age group was the most common age group in newly diagnosed T1DM. Malaise, polyuria, polydipsia, weight loss are most seen symptoms in newly diagnosed patients. Vomiting is the most common symptom in formerly diagnosed T1DM patients. Time period before PICU admission was longer in newly diagnosed T1DM. Hypophosphatemia is common in PICU admission. Hypokalemia was mostly seen in DKA in newly diagnosed T1DM patients. Diagnostic tools of brain edema should be more effectively used in PICU. There should be educations or commercials for school age group to provide public awareness for DM. Formerly diagnosed adolescent patients should have strict control for DKA and doctors should be more cautious about their parental education for DM.

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