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Differences in Children with Type 1 Diabetes Aged ≤6 and >6 Years at the Time of Diagnosis

Tip 1 Diyabetli 6 Yaştan Küçük ve Büyük Çocukların Tanı Anındaki Farklılıkları

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ABSTRACT

Objective: There has recently been an increase in the incidence of Type 1 diabetes mellitus (T1DM), particularly among younger children. The purpose of the present study was to analyze the differences in the clinical and laboratory findings at presentation between the younger (≤6 years of age) and older (>6 years of age) groups of patients with T1DM.

Material and Methods: A retrospective scan was performed on the hospital data of 99 children with T1DM registered during the past 10 years at the pediatric endocrinology clinic of Ankara Children's Haematology Oncology Training Hospital (49 patients were ≤6 years old and 50 were >6 years old). The clinical and laboratory findings at the first presentation to the clinic were reviewed.

Results: The mean duration of symptoms before presentation was shorter (15.2±1.9 and 27.7±5.1 days respectively) in the younger age group. The transition time from intravenous insulin to subcutaneous treatment was significantly longer than in the older patients (17.1±1.3 and 13.6±1.2 hours respectively). Weight loss was found to be more significant among older children and HbA1c was significantly lower in the younger age group. A significantly higher proportion of patients in the younger group was found to be positive for at least one of the diabetes-associated antibodies ($p<0.05$).

Conclusion: Elucidation of clinical and laboratory differences between younger and older diabetic children at the time of diagnosis would provide guidance for diabetes care teams in the diagnosis, treatment and monitoring of these patients.

Key Words: Child, HbA1c, Ketoacidosis, Type 1 diabetes mellitus

ÖZET

Amaç: Son zamanlarda özellikle 6 yaş altındaki çocuklarda Tip 1 diabetes mellitus (T1DM) insidansında artış olmuştur. Bu çalışmanın amacı, küçük yaş ve daha büyük yaşlardaki T1DM'lu çocukların tanı anındaki klinik ve laboratuvar farklılıklarını analiz etmektir.

Gereç ve Yöntemler: Ankara Çocuk Sağlığı Hastalıkları Hematoloji Onkoloji Hastanesi pediatrik endokrin bölümünde geçen 10 yılda T1DM tanısı alan 99 çocuğun dosyası (49 hasta ≤6 yaş, 50 hasta >6 yaş) geriye dönük incelendi. Kliniğe ilk başvuru anındaki klinik ve laboratuvar bulguları değerlendirildi.

Bulgular: Yaşça küçük olan grupta, ortalama semptomların ortaya çıkış süresi daha kısa (15.2±1.9 ve 27.7±5.1 gün) ancak insülin infüzyonundan subkutan insülin geçiş süresi daha uzun (17.1±1.3 ve 13.6±1.2 saat)'di. Kilo kaybı semptomu büyük çocuklarda daha sık ve HbA1c düzeyi küçük çocuklarda anlamlı olarak daha düşüktü. Küçük çocuklarda diyabet ilişkili antikorlardan en az birinde pozitiflik anlamlı olarak daha fazlaydı ($p<0,05$).

Sonuç: Bu çalışma, küçük ve daha büyük yaştaki diyabetik çocukların hastaneye ilk başvuru anındaki klinik ve laboratuvar bulgularındaki farklılıkları göstermektedir ve bu farklılıkların ortaya konması, diyabet ekibinin bu hastaların tanı, tedavi ve izleminde yol gösterici olacaktır.

Anahtar Sözcükler: Çocuk, HbA1c, Ketoasidoz, Tip 1 diyabetes mellitus

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INTRODUCTION

Type 1 diabetes mellitus is one of the most common chronic conditions of childhood and genetic, autoimmune and environmental factors are held responsible for its aetiopathogenesis. There has been a growing incidence of T1DM, particularly notable after the second half of the 20th century. Socioeconomic factors as well as environmental and genetic aspects are known to be involved in the differences of this increasing prevalence both between and within countries (1-4). A study by the European Diabetes Study Group (EURODIAB) on T1DM diabetic children younger than 16 years of age that was conducted between 1989 and 2003 with the participation of 17 European countries reported a mean annual increase of 3.9% in prevalence, with the largest increase being 5.4% as found in the 0-4 age group. Accordingly, it is anticipated that the number of diabetic children ≤5 years old will double between 2005 and 2020 (5).

Children with T1DM younger than 6 years of age constitute a very specific subpopulation among the overall diabetic population. Findings are less pronounced at the onset of diabetes, but progress faster and may be mistaken for other conditions. Diet, exercise and insulin therapy may present significant challenges in the long term. Patients of this age group are more susceptible to hypo- and hyperglycaemia, their diets are more labile, and they are physically more active than other age groups. Fluctuations between fasting and postprandial blood glucose levels are therefore more common in this population. Diabetics aged 6 years and younger represent the second most challenging group of patients after adolescents, in achieving metabolic control (6-8). Awareness of the characteristics and differences specific to these patients will ensure an informed first step in developing a suitable treatment plan and achieving metabolic control.

MATERIAL and METHODS

The Study Group

The present study was performed at the Paediatric Endocrinology Clinic of Ankara Children's Haematology Oncology Training Hospital between January 2000 and February 2011 on 99 patients diagnosed with T1DM. All patients aged 6 years or younger (n=49) with sufficient information on their files were included in the study and formed Group 1. To enable comparisons of clinical and laboratory data, 50 patients older than 6 years of age diagnosed during the same period were randomly selected and formed Group 2. The clinical, laboratory and therapeutic data that were recorded in the patient files were retrospectively reviewed. Those diagnosed with T1DM at another healthcare centre or those with missing file information were excluded.

Collecting and Interpreting the Data

Clinical symptoms (nausea/vomiting, abdominal pain, altered consciousness, weight loss, loss of appetite) at the time of diagnosis and their duration were recorded. The presence of diabetic ketoacidosis, ketosis or hyperglycaemia was also recorded.

Diabetic ketoacidosis was defined as venous blood gas measurement of pH<7.30 and HCO3<15 mEq/L with accompanying blood glucose level of 250 mg/dL, blood ketone result of above 3.5 mmol/L or high positive levels of urinary ketone and glucose in addition to the pre-existing diabetic symptoms (1,2).

Diabetic ketosis was defined as positive ketone in blood and urine accompanied by hyperglycemia in addition to diabetic symptoms in the absence of acidosis (1,2).

Hyperglycaemia was defined as blood glucose levels of >200 mg/dl in the absence of acidosis or ketosis in addition to usual diabetic symptoms (1-3).

Time to switch from intravenous insulin therapy to subcutaneous insulin was calculated based on the files of patients who presented with diabetic ketoacidosis and diabetic ketosis. Insulin and C-peptide levels and hemoglobineA1c (HbA1c) measurements at the time of diagnosis were also taken into account. For autoimmunity, insulin autoantibody (IAA), glutamic acid decarboxylase antibody (GADA), and islet cell antibody (ICA), the values were recorded from patient files and were classified as positive or negative. Diabetes-associated antibodies (excluding ICA) and celiac antibodies were studied by using ELISA, while ICA was studied by immunofluorescence (EuroimmunTM). Results were classified as positive or negative.

Statistic Analysis

Statistical analysis of the data was performed using "The Statistical Package for the Social Sciences 17.0 (SPSS, Inc. Chicago IL, USA, Microsoft)". Students' t-test was used for comparison of numeric data and the chi-square test was used for non-numeric data. Correlations between dependent and non-dependent variables were studied using Pearson's correlation analysis. Results were presented as mean± standard deviation, and mean ± SEM (standard error of mean) was used for data with high variability. Statistical significance was set at $p<0.05$.

RESULTS

The patients were divided into two groups; aged ≤6 years (n=49) and >6 years (n=50). Their clinical findings at the time of presentation are provided in Table I. Duration of diabetic symptoms was shorter in Group 1, while the patients in Group 2 experienced more weight loss before admission to the hospital. There was a positive association between symptom duration

and age (r=0.29, p=0.004). The patients did not differ quantitatively in terms of concomitant conditions (ketoacidosis, ketosis, hyperglycaemia).

The two groups did not differ significantly in blood glucose, venous pH, and blood ketone values measured at the time of presentation while bicarbonate levels were significantly lower in Group 1 (p=0.031). Insulin and C-peptide levels were not different between the groups while mean HbA1c levels were significantly lower in Group 1. The differences between the groups in laboratory measurements are provided in Table II.

Duration of intravenous treatment revealed a significantly longer duration for Group 1 (p=0.035).

The distribution of GADA, IAA and ICA positivity at the time of presentation is presented in Table III.

Twenty-two (44%) patients in Group 1 and 16 (32%) in Group 2 were positive for at least one autoantibody and a statistically significant difference was noted between the groups (p<0.05).

Table I: Clinical features of the diabetic children at the time of diagnosis.

	Group 1 (≤6 years) n=49	Group 2 (>6 years) n=50	p value
Age at diagnosis (years)	3.7± 1.5	10.4±2.7	
Gender (F/M)	25/24	26/24	NS*
Symptom duration (days)	15.2±1.9	27.7±5.1	0.025
Complaints at presentation, n (%)			
Loss of appetite	13 (26)	9 (18)	NS
Abdominal pain	10 (20)	14 (28)	NS
Weight loss	19 (38)	38 (76)	0.001
Nausea/vomiting	13 (26)	14 (28)	NS
Altered consciousness	11 (22)	8 (16)	NS
Concomitant disease at presentation, n (%)			
Ketoacidosis	34 (68)	27 (54)	NS
Ketosis	11 (22)	15 (30)	NS
Hyperglycaemia	4 (8)	8 (16)	NS

NS: *non-significant,* ***F:*** *female,* ***M:*** *male.*

Table II: Laboratory findings of the groups at the time of diagnosis.

	Group 1 (≤6 years) n=49	Group 2 (>6 years) n=50	p value
Blood glucose (mg/dl)	479.0±22	520.7±24.5	NS*
pH	7.21±0.1	7.24±0.1	NS
Bicarbonate (mmol/L)	10.8±0.9	13.9±1.2	0.031
Ketone (mmol/L)	3.6±0.2	3.8±0.2	NS
Insulin (IU/ml)	3.1±0.4	2.4±0.2	NS
C-peptide (ng/ml)	0.5±0.1	0.5±0.2	NS
HbA1c (%)	9.6±2.0	11.8±2.6	0.0001

NS: *non-significant,* ***HbA1c:*** *hemoglobin A1c.*

Table III: Diabetes-related autoantibody positivity in the groups [n (%)].

Autoantibodies	Group 1 (≤6 years) n=49	Group 2 (>6 years) n=50	p value
GADA	15 (30.6)	12 (24.0)	>0.05
IAA	9 (18.3)	5 (10.0)	
ICA	13 (26.5)	10 (20)	

GADA= *glutamic acid decarboxylase antibody,* ***IAA=*** *Insulin autoantibody,* ***ICA=*** *Islet cell autoantibody.*

DISCUSSION

The present study demonstrated that children with T1DM aged 6 and younger who had been diagnosed during a period of 10 years at the Paediatric Endocrinology Clinic of Ankara Children's Haematology Oncology Training Hospital, sought medical attention earlier following the onset of symptoms, had lower levels of HbA1c, required longer intravenous fluid therapy and a higher proportion of these children had autoantibody positivity.

At the time of presentation, the most common complaints included polyuria, weight loss, nausea/vomiting and abdominal pain. There was a significant difference between the groups for weight loss. Nineteen percent of the patients in the younger group and 38% in the older group had experienced weight loss. This inter-group difference was attributed to the fact that the time to admission to a healthcare institution was shorter following the onset of diabetic symptoms with decreasing age. Type 1 diabetes typically has an abrupt onset following a period of 2-3 weeks. There may however, be variations in the duration of symptoms ranging from 1 to 180 days (8,9). A study from Sweden between 1997 and 2001 reported that 38% of the subjects had complaint durations shorter than 8 days and 46% of these subjects were in the group of diabetic patients younger than 5 years of age (10). The duration of symptoms in the present study was 15 days on average in Group 1 and 27 days in Group 2, with a significant difference between the groups. There was also a positive correlation between age and symptom duration. The shorter symptom duration with decreasing age was attributed to the fast progression of diabetes in younger children.

The frequency of accompanying diabetic ketoacidosis (DKA) at the time of diagnosis varies by geographical region. Higher quality of available healthcare services and increased levels of education and awareness of families are associated with decreasing frequency of ketoacidosis (11). According to the reports of EURODIAB ACE Study Group concerning 24 centres in Europe covering a population of 15 million, about 40% of 1260 patients with newly-diagnosed type 1 DM presented with DKA, whereas the ratios reported from different centres vary between 26% and 87%. The presence of DKA on admission is reported to be less common in countries with higher standards of life and healthcare (12). Previous studies have described a higher frequency of DKA at presentation for patients younger than 5 years of age compared to older patients (13-15). In our study, 61% of the patients had DKA at the time of presentation; this rate was 68% in the group of patients equal or younger than 6 years of age while it was 54% in the other group. Bicarbonate levels were lower in the younger group, and the proportion of patients with ketoacidosis at the time of presentation was also higher in this group. The lack of statistical significance difference between the two groups in the rate of ketoacidosis at the time of presentation was attributed to the limited number of patients studied.

We found the time required to switch intravenous fluid and insulin to subcutaneous insulin therapy to be significantly longer in the patients 6 years of age or younger. This was attributed to the longer time needed to recover from deteriorated metabolic balance in the younger children with T1DM.

There were no differences between our groups in terms of insulin and C-peptide values at the time of presentation. Pozzilli et al. (15) evaluated 235 newly-diagnosed diabetic patients and found basal insulin levels of subjects younger than 7 years of age to be lower than those of the others. Another study from Italy reviewed 66 diabetic patients retrospectively and found no relationshipsbetween baseline c-peptide values and the clinical status. The study also reported that C-peptide had no impact on long-term metabolic control (16).

HbA1c measurements are important for routine monitoring of diabetes and for assessing the associations between plasma glucose control and complications. Decreased levels of HbA1c levels have also been reported from the same geographical regions for different periods of time and this is donsistent with the recent decrease in the incidence of DKA (17). We identified a significant difference in HbA1c levels between the groups. Mean HbA1c was lower in patients 6 years of age or younger, and this was attributed to the short time from the onset of symptoms to the diagnosis.

The majority of patients with newly-diagnosed type I diabetes were positive for at least one of the diabetes-related autoantibodies, i.e., ICA, GADA and IAA (1,2). Theoretically, patients developing T1DM in early childhood are expected to undergo a more rapid autoimmune process and to be positive for antibodies more frequently than others. The most typical example is a study from Finland by Komulainen et al. (18) on 620 children with diabetes. They reported that 100% of patients younger than 2 years of age, 99.2% of those between 2 and 5 years, and 97.4% of those above the age of 5 were positive for at least one antibody, and suggested a strong beta-cell autoimmune attack in very young patients with newly-diagnosed diabetes (18). Other studies, however, have reported that a small proportion of young patients with diabetes were positive for diabetes-associated antibodies. Hatout et al. (19) reported lower levels of ICA and GADA, and Feeney et al. (20) reported lower levels of GADA and IA-2A in patients diagnosed when younger than 5 years old. Urakami et al. (21) reported that diabetes might have developed due to non-immune mechanisms in younger Japanese patients with newly-diagnosed T1DM. This might suggest that the antibody distribution and intensity may vary across countries. In our study group, GADA, ICA and IAA were positive in 40, 35 and 20% of the children, respectively. GADA was the antibody with the most frequent positive results in both groups. Assessment of the frequency of antibody positivity showed that 62.8% of the patients who were 6 years of age or younger were positive for at least one antibody, and this was significantly higher compared to the other group. This suggested a more aggressive autoimmune process in younger children in our study group.

In conclusion, the prevalence of newly-diagnosed T1DM patients is increasing and an increasing number of children with T1DM has been observed in the past 20 years. It is important to understand the characteristics specific to this population. The results of our study suggest a faster clinical process and longer duration of treatment with intravenous fluid and insulin therapy in younger diabetic children. Close monitoring is necessary in this group since they have a high risk of mortality. Raising awareness of diabetic symptoms in the society and among healthcare professionals will help to ensure the early diagnosis of T1DM before severe ketoacidosis develops.

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