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RESEARCH ARTICLE

An evaluation of clinical and epidemiological characteristics and autoantibody status of children with type 1 diabetes mellitus at presentation

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ABSTRACT

Aim: The purpose of this study was to examine clinical and epidemiological characteristics and autoantibody status of children diagnosed with type 1 diabetes mellitus (DM) at presentation.

Methods: The data retrieved from the medical records of 80 patients with type 1 DM, aged under 18 and diagnosed at the Adıyaman Education and Research Hospital, pediatric endocrinology clinic and emergency department between September 2016 and December 2021 were examined retrospectively. Patients' symptoms at presentation and clinical and laboratory findings were recorded.

Results: Thirty-four (42.5%) of the children with type 1 DM were girls and 46 (57.5%) were boys, with a mean age of 10.69±4.75 years. The presentation was most common in the 5-10 (33.8%) and 10-15 (31.3%) age groups. Diabetic ketoacidosis (DKA) was present in 36 (45%) of the children with type 1 DM at presentation, ketosis without acidosis in 30 (38%), and only hyperglycemia in 14. Sixty percent of the patients under five years of age, 48% of those in the 5-10 age group, and 33.3% of the 10-18 age group presented with DKA, and the frequency of presentation with DKA was higher among patients under five years of age than in the other age groups. Severe DKA findings were present in 13 (36%) cases, moderate findings in 10 (27.8%), and mild findings in 13 (36.1%). Anti-glutamic acid decarboxylase positivity was present in 14 cases (53.2%), islet cell antibody positivity in 37 (48%), and anti-insulin antibody positivity in 11 (14.2%).

Conclusion: The incidence rate of DKA in children with newly diagnosed type 1 DM and the rate of severe ketoacidosis among them are quite high in the province of Adıyaman. This shows the need to continue diabetes awareness programs and to reach a larger number of people.

Keywords: children, diabetic ketoacidosis, type 1 diabetes mellitus

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INTRODUCTION

Type 1 diabetes mellitus (DM) is a chronic, progressive disease that progresses with the destruction of pancreatic beta cells, resulting in insufficient insulin secretion, and is mostly seen in the pediatric age group (1). It represents 85% or more of all cases of diabetes in young people under 20 years of age worldwide (2). It exhibits two important peaks in childhood, at 4-6 years and 10-14 years. The first peak is thought to be due to infections, which increase with the start of school, and the second peak is due to increased sex hormones, growth hormone, and psychological stress during puberty (3).

The American Diabetes Association divides the disease into two groups, type A (immune-mediated diabetes [IDM]) and type B (idiopathic diabetes) (4). An autoimmune response to beta cells is observed in 90% of cases of type 1 diabetes, while idiopathic deficiency in beta cells is present in 10% of cases. IDM results from T cell-mediated autoimmune destruction of β-cells (5). Various autoantibodies, such as insulin autoantibodies, islet cell autoantibodies, anti-insulin autoantibodies, glutamic acid decarboxylase antibodies, tyrosine phosphatase antibodies (IA_2), and zinc transporter antibodies (ZnT8A) are implicated in the immune destruction of β-cells (6). This autoimmune destruction of beta cells eventually leads to the clinical findings of diabetes by causing a gradual decrease in insulin secretion. Children with type 1 diabetes are at a greater risk of other autoimmune diseases than healthy children (7). A significant proportion of children and adolescents with type 1 diabetes have detectable organ-specific autoantibodies in addition to pancreatic autoantibodies, and other accompanying autoimmune diseases are present in approximately 25% of patients with type 1 diabetes. The autoimmune diseases most frequently seen in patients with type 1 diabetes is thyroiditis, followed by celiac disease (8).

The purpose of this study was to examine the autoimmune status and clinical and epidemiological characteristics at presentation in children diagnosed with type 1 DM in the Adıyaman Education and Research Hospital pediatric endocrinology clinic or pediatric emergency department, Turkey.

MATERIAL AND METHODS

Data retrieved from the medical records of 80 patients with type 1 diabetes, younger than 18 years of age, diagnosed in the pediatric endocrinology clinic or pediatric emergency department of Adıyaman Education and Research Hospital between September 2016 and December 2021 were analyzed retrospectively. The approval for the study was granted by the Adıyaman University Non-Interventional Research Ethical Committee (decision no. 2021/02-9 dated 16/02/2021).

The diagnosis of type 1 DM was based on the International Society for Pediatric and Adolescent Diabetes criteria (9). Patients' symptoms at presentation, clinical findings, biochemical values, ketone measurements in blood and urine, pancreatic autoantibodies (anti-GAD, islet cell antibody, and anti-insulin autoantibody), C-peptide levels, and venous blood gas results were evaluated. pH <7.3 and/or HCO3 <15 mmol/L in venous blood gas together with hyperglycemia, ketonemia, or ketonuria were defined as diabetic ketoacidosis (DKA). Cases with DKA were divided into three groups, mild, moderate, and severe, based on their pH and HCO3 levels (10). Under that classification, pH 7.2-7.3 or HCO3 10-15 mmol/L were considered mild, pH 7.1-7.2 or HCO3 5-10 mmol/L moderate, and pH<7.1 or HCO3<5 mmol/L severe DKA.

Free T4 and TSH anti-thyroglobulin and anti-thyroid peroxidase antibody levels were investigated in relation to autoimmune thyroid diseases that may accompany type 1 diabetes, anti-tissue transglutaminase (tTG) IgA, and IgG levels were investigated in relation to celiac disease. Free T4 and TSH levels within normal reference ranges were considered euthyroidism, low free T4 and high TSH levels as hypothyroidism, normal sT4 and high TSH as subclinical hypothyroidism, high free T3 and high free T4 were regarded as hyperthyroidism. TSH, fT4, fT3, thyroid peroxidase antibodies, and thyroglobulin antibodies were studied using commercial kits. These tests were performed using electrochemiluminescence assay on a Beckman Coulter DxI800 device with an appropriate kit (Beckman Coulter Access kit, USA). Values above 4.18 IU/mL for Anti-TG and 5.61 IU/mL for anti-TPO

were considered positive. Anti-tTG IgA and IgG levels were analyzed using ELISA REF EIA 31003 and 31004 kits (Euroimmune, Germany). Anti-tTG IgA or anti-tTG IgG ≥15 U/ml reference threshold levels were considered seropositive. The results of the cases with celiac autoantibody levels three or more times higher than the reference threshold value and diagnosed with celiac disease based on upper gastrointestinal endoscopy and biopsy were recorded (11).

Statistical analysis

The research data were analyzed on SPSS Windows 15.0 software. Continuous variables were expressed as mean plus standard deviation, and categorical variables as numbers and percentages.

The chi-square test was applied to compare categorical data. The normality of the data distribution was examined using the Kolmogorov-Smirnov test. In the case of normal distribution, the independent groups t-test was used to compare two independent groups.

RESULTS

Eighty patients, 34 (42.5%) girls and 46 (57.5%) boys, diagnosed with type 1 DM at the Adıyaman Education and Research Hospital between September 2016 and December 2020 were included in the study. Boys outnumbered girls among the newly diagnosed patients with type 1 DM, with a male to female ratio of 1.3:1. The mean age of the patients was 10.69±4.75 years, and there was no significant age difference between the genders (p= 0,365) (Table 1). The presentation was most frequent in the 5-10 age group (33.8%), followed by the 10-15 (31.3%), 0-5 (25%), and 15-18 (10%) age group (Table 2). Thirty-five percent of the patients were diagnosed in winter, 32.5% in the fall, 17.5% in spring, and 13.8% in summer.

Thirty-one patients presented to the clinic with polyuria and polydipsia, 14 with clouded consciousness, 13 with weight loss, 12 with lack of appetite and lethargy, and nine with other non-specific symptoms, while one patient presented for routine screening (Table 2).

DKA was present at the time of the presentation in 36 (45%) of the children with type 1 DM included in the study, ketosis without acidosis in 30 (38%) and hyperglycemia in 14 (17.5%). The patients' laboratory results at the time of the diagnosis are shown in Table 1. Severe DKA was present in 13 (36%) patients, moderate DKA in 10 (27.8%), and mild DKA in 13 (36.1%). No significant difference in the mean HbA1c levels was observed among the cases presenting with DKA and those of patients without DKA at the time of the presentation (p=0,851) (Table 3). Sixteen (44.5%) of the patients presenting with DKA were girls, and 30 (55.5%) were boys. No significant difference was determined in terms of gender (chi-square p: 0.101). In terms of age groups, 60% of patients under five years of age, 48% of those aged between 5-10, and 44% of those aged between 10-15 presented with DKA. None of the patients in the 15-18 age group presented with DKA, and the highest incidence rate of DKA was observed in the children group under five years of age (p=0.017) (Table 4). There was a family history of type 1 DM in seven (9%) cases, type 2 DM in 35 (43.8%),

Table 1. Patients' age distribution and laboratory findings at presentation

Gender	Mean	SD	Minimum	Maximum
Age of female patients' (year)*	9,1	4,4	1,5	15,4
Age of male patients' (year)*	11,8	4,7	2,4	17
Serum Glucose (mg/dL)	487,18	191,65	145	811
HbA1c	12,43	2,61	7,3	18
Serum C-peptide (ng/mL)	0,45	0,42	0,10	2,44
Venous blood pH	7,23	0,15	6,78	7,41
Venous blood HCO3 (mmol/L)	14,21	6,93	2,4	25,2
Venous blood pCO2 (mmHg)	27,34	10,47	8	46

*İndependent samples t-test (p=0,365)

Table 2. Distribution of some characteristics of the patients

	n	%
Application age		
0-5 age	20	25
5-10 age	27	33,8
10-15 age	25	31,2
15-18 age	8	10
Application complaint		
Polyuria-polydipsia	31	38,75
Clouding of consciousness	14	17,5
Weight loss	13	16,25
Lack of appetite and fatigue	12	15
Nausea and vomiting	4	5
Dry mouth	2	2,5
Abdominal pain	2	2,5
Tiredness	1	1,25
Routine examination	1	1,25
Autoantibody Positivity in Female		
Anti GAD	22	66,7
Anti insulin antibody	7	21,7
Islet cell antibody	17	51,5
Autoantibody Positivity in Male		
Anti GAD	19	44,2
Anti insulin antibody	4	9,3
Islet cell antibody	20	46,5

Anti GAD: anti-glutamic acid decarboxylase

Table 3. Comparison of patients' initial HbA1c levels according to presentation with DKA

Initial Application Table	n	HbA1c Mean±SD	p value*
DKA	14	12,65±2,61	0,851
Non-DKA	66	12,25±2,62	

DKA: Diabetic ketoacidosis *İndependent samples t-test

and both type 1 and type 2 DM in seven (9%) cases. Thirty-six cases had no family history of diabetes. The incidence of presentation with DKA was significantly lower among children with a family history of diabetes compared to those with no such family history (p=0,005) (Table 4).

Autoantibody status

Analysis of pancreatic autoantibodies revealed anti-GAD positivity in 41 (53.2%) cases, islet cell antibody positivity in 37 (48%), and anti-insulin antibody positivity in 11 (14.2%). No autoantibody positivity was observed in 18 (22.5%) cases. Three patients' autoantibody values were unavailable. While no statistically significant difference was observed for all pancreatic autoantibodies, the autoantibody positivity rate was higher in girls than in boys (Table 2). Anti-GAD positivity was 66.6% in girls and 44.2% in boys (p=0.05), anti-insulin antibody positivity was 21.2% in girls and 9.3% in boys (p=0.144), and islet antibody positivity was 51.5% in girls and 46.55 in boys (p=0.665). No association was found between autoantibody positivity, age at diagnosis, or C-peptide levels and presentation with DKA (p=0.473, p=0.580, and p=0.827, respectively).

Patients with type 1 DM were also screened for other potential accompanying autoimmune diseases at the time of the diagnosis. When the patients were evaluated for chronic autoimmune thyroiditis, anti-TPO positivity was detected in seven (8.8%), and anti-thyroglobulin positivity in four (5%). Hypothyroidism was present in only one case with autoantibody positivity. A screening for celiac , which is another autoimmune disease, was also carried out. Anti-tTG IGA positivity was present in 21 (26.3%) cases and anti-tTG IgG positivity in 15 (18.8%). Celiac disease was diagnosed in eight (10%) of the cases with celiac antibody positivity. Two patients with negative celiac autoantibodies at presentation became positive in the subsequent months, and celiac disease was diagnosed after biopsy. Three patients with initial mildly positive autoantibodies were found to be celiac antibody negative during the investigation after six months.

Table 4. Relationships between presence of DKA at initial presentation and age and familial history of diabetes mellitus

	DKA (+)		DKA (-)		p value
Age group	**n**	**%**	**n**	**%**	
0-5 age	12	60	78	40	**0,017**
5-10 age	13	48,1	14	51,9	
10-15 age	11	44	14	56	
15-18 age	0	0	8	100	
DM in the family					
Tip 1 DM	4	28,6	10	71,4	**0,005**
Tip 2 DM	11	31,4	24	68,6	
No diabetes	10	67,7	21	32,3	

DM: Diabetes Mellitus, DKA: Diabetic ketoacidosis

DISCUSSION

This study was conducted in the province of Adıyaman in the southeast of Türkiye and is important in terms of examining the immediate clinical and epidemiological characteristics and autoantibody status of children with type 1 diabetes in the region.

The mean age at diagnosis of the children with type 1 DM in this study was 10.69±4.75 years. Presentation was most common in the 5-10 year age group, followed by the 10-15 year age group. Differences between age groups have also been observed in other studies. Studies from Sweden and Finland, where type 1 diabetes is frequently seen, have reported a peak in the 5-9 age group (12,13). Studies from Türkiye have also identified the ages at which type 1 diabetes is frequently seen. In another study of 1079 children with type 1 DM in the Turkish province of Izmir, the mean age at diagnosis was 7.78 years, and presentation was most frequent in the 4-12 age group (14). A study from Northwest Türkiye investigating the incidence of type 1 DM reported that presentation was most common in the 5-14 year age group, followed by the 15-17 year age group (15).

Type 1 DM exhibits gender differences. Male dominance has been reported in countries with a greater incidence of type 1 diabetes, and female dominance in those with a lower incidence (16-18). A study from Sweden reported no gender difference in the incidence of type 1 diabetes between the ages of 0 and 14, but that male dominance emerged at 15-40 years of age (19). This gender difference has been attributed to greater peripheral insulin resistance in males and to hormonal effects. Poyrazoğlu et al. reported male dominance in children under 18 years of age with type 1 DM, except in the 5-9 age group, in which female gender was dominant (15). Similarly, Svensen et al. found male dominance in children with type 1 DM in the 0-14 age group in Denmark (16). Although autoimmune diseases are more common in girls, studies have shown that type 1 diabetes has a greater effect on boys. Consistent with the previous literature, male gender dominance was also observed in newly diagnosed children with type 1 DM in the present study.

Several studies have shown a seasonal association with the time of diagnosis of type 1 DM. A study from Greece involving 105 children with type 1 DM, aged between one and 16 years, found that the diagnosis was made in cold, rainy months such as March and October (20). Another study from the city of Medina in Saudi Arabia, where the average temperature in spring and summer is 40 degrees Celsius, also reported that more patients were diagnosed in the fall and winter, which are relatively cooler than the summer (21). This seasonal correlation has also been supported by extensive studies. Research by the SWEET study group involving 203,603 patients with type 1 DM documented that rates of diagnosis were higher in the fall and winter and lower in the spring and summer,

while no variation was observed in terms of gender or geographical latitude (22). Attempts have been made to explain the relationship between diagnosis of diabetes and seasonal variations in terms of such factors such as exposure to viral infections, changes in physical activity, school stress, and changes in vitamin D synthesis. Consistent with the previous literature, in the province of Adıyaman, with its warm and rainy winters and hot and dry summers, this study showed that presentations with type 1 DM were also more frequent in the fall and winter in this study.

The most common symptoms at time of diagnosis in children with type 1 DM are polyuria, polydipsia, weight loss, and fatigue (23). The most common complaints at presentation in the present study were polyuria-polydipsia (39%), blurred consciousness (18%), and weight loss (16%). Clinical symptoms in type 1 diabetes generally commence 2-3 weeks before diagnosis. Some studies have shown that the time to onset of symptoms is even shorter in very young children (24,25). Diagnosis may be delayed since these symptoms are non-specific, and DKA, a fatal complication, may be the first reason for presentation (26). The incidence of DKA at the time of diagnosis in studies from Türkiye ranges between 41% and 65% (12,27). Germany and Sweden, countries with higher socio-economic levels, reported rates of 20% and 19.5% respectively (26,28). Despite the awareness campaigns aimed at preventing DKA, data from 13 developed countries showed that the incidence of DKA at the time of diagnosis in children with type 1 DM increased slightly between 2006 and 2016 (26). Another international study reported that incidence of ketoacidosis in children with type 1 diabetes was 30% in 2002-2010 and increased to 38.5% in 2010-2016 (29). Similarly, a study from the Aegean region of Turkey reported that the incidence of DKA at the time of diagnosis was 36.4% in 1999-2014 and subsequently increased to 46.5% (30). In the present study, the incidence of DKA at the time of the diagnosis was 45%. The incidence rate of presentations with DKA in our province reflects the data from Türkiye. However, it exceeds the figures reported for developed countries. Cases of severe DKA accounted for 36% of all patients presenting with DKA at the time of diagnosis. A study of 41,189 newly diagnosed cases of type 1 DM in Germany reported that only 6.1% of them involved severe DKA (28), which is much lower than the figure in our region. Various studies have shown that living in countries with a high incidence rate of type 1 diabetes and having a family history of type 1 diabetes reduce the rate of presentation with DKA, whereas being younger than five years of age and having a low socioeconomic level increase the risk of presentation with DKA (31,32). Segerer et al. determined a higher incidence of ketoacidosis at the time of diagnosis in young children compared to older children and adolescents and attributed the difference to the difficulty in interpreting clinical symptoms and findings in young children (28). In the present study, the rate of presentation at time of diagnosis in children under five with type 1 DM was approximately 60%, higher than in the other age groups. Awareness of the symptoms of diabetes may reduce the rate of presentation with DKA by allowing early recognition of the disease. The rate of presentation with DKA at the time of diagnosis and the incidence of severe DKA, both of which were being high in the present study, may be related to low socioeconomic status and difficulties accessing health services in these families.

Studies have found pancreatic autoantibody positivity in approximately 80-90% of children newly diagnosed with type 1 DM (33,34). In a study of 757 patients under the age of 15 newly diagnosed with type 1 DM, Sabbah et al. reported anti-GAD positivity in 73.2% of cases, IA-AA positivity in 85.7%, IAA positivity in 54.2%, and multiple autoantibody positivity in 72.6% (35). Children with multiple autoantibody positivity in that study were younger than the others, had lower serum C-peptide levels at the time of diagnosis, and had higher daily insulin needs at 12-, 18-, and 24-months of follow-up. Based on their findings, Sabbah et al. hypothesized that diabetes-associated multiple autoantibody positivity accelerates pancreatic b-cell destruction and is also associated with increased exogenous insulin requirements in the second year of the disease (35). Pancreatic autoantibody positivity was present in 78% of the cases in the present study. The most common was anti-GAD antibody positivity (51.2%), followed by islet cell antibody positivity (46.3%) and anti-insulin antibody (13.8%) positivity. Single autoantibody positivity was present in 49% of cases, double autoantibody positivity in 40%, and triple autoantibody positivity in 5%. No relationship was

determined between autoantibody positivity and age at diagnosis, C-peptide levels, or presentation with a manifestation of DKA.

Type 1 DM may be comorbid with other autoimmune diseases. Autoimmune thyroiditis is one of the most common immunological disorders in patients with type 1 DM, with rates of thyroid autoantibodies ranging between 3% and 50% (36). Jung et al. reported a rate of 26% in their study of children newly diagnosed with type 1 DM (37). Analysis of our patients for chronic immune thyroiditis at presentation revealed anti-TPO positivity in seven (8.8%) cases and anti-thyroglobulin positivity in four (5%). Hypothyroidism was diagnosed in only one of these cases, and thyroid hormone therapy was initiated. Accompanying celiac antibody positivity may also be seen in children with type 1 DM at the time of diagnosis. In their study of 425 newly diagnosed children with type 1 DM, Rinawi et al. determined anti-tTG antibody elevation in 34 children (8%), of whom 14 were diagnosed with celiac disease after biopsy (38). In the present study, anti-tTG IGA positivity was observed in 21 (26.3%) and anti-tTG IgG positivity in 15 (18.8%) cases at presentation, which are higher than those reported by Rinawi et al. Eight of these cases were diagnosed with celiac disease after biopsy (38). In two patients with negative autoantibodies at presentation, autoantibodies became positive in the following months and celiac disease was diagnosed after biopsy. In addition, Rinawi et al. reported an initial mild anti-tTG positivity in 13 patients, which normalized over time (38). Similarly, in the present study, antibody levels investigated after six months were found to have normalized in three patients with an initial mild autoantibody elevation. This finding shows that patients with mild anti-tTG antibody elevation at baseline should not be rushed into a gluten-free diet.

The main limitations of this study are its single-center nature and the small number of cases. However, this study is particularly valuable in presenting four years of type 1 DM data for our region.

In conclusion, the average rate of presentation with DKA in children newly diagnosed with type 1 DM in the province of Adıyaman is 45%, but is as high as 60% in children under the age of five. In addition, the rate of severe ketoacidosis among cases presenting with DKA is quite high. Continuing of diabetes awareness programs and raising awareness of families and society about diabetes symptoms can reduce the incidence of this important complication of type 1 diabetes. Screening newly diagnosed children with Type 1 DM for other autoimmune diseases such as Hashimoto's thyroiditis and celiac disease is important for early diagnosis and treatment.

Ethical approval

This study has been approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval date 16.02.2021, number 2021/02-9). Written informed consent was obtained from the participants.

Author contribution

Concept: SB, AA; Data Collection or Processing: SB, AA; Analysis or Interpretation: İHB, AA; Literature Search: SB, AA, İHB; Writing: SB, AA, İHB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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