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Research

Clinical Features of Children and Adolescents at the Onset of Diabetes: A Single-center Experience

Diyabetli Çocuk ve Ergenlerin Tanıdaki Klinik Özellikleri: Tek Merkez Deneyimi

Saygın Abalı[1], Yasemin Akın[2]

[1]Acıbadem Mehmet Ali Aydınlar University School of Medicine, Department of Pediatrics, Pediatric Endocrinology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Pediatrics, İstanbul, Türkiye

ABSTRACT

Objective: This study evaluated the findings of pediatric cases with diabetes mellitus (DM) who were admitted to a pediatric endocrinology unit for two years.

Methods: In this retrospective, observational study, children and adolescents aged 0-18 years, were diagnosed with DM were evaluated. Cases were grouped as formerly diagnosed and new-onset. Demographic and laboratory features at admission were recorded. The type of diabetes was classified and, also the presence of diabetic ketoacidosis (DKA) and severe DKA was described according to the current criteria.

Results: The mean age of 108 children (51 girls) at the time of the first evaluation in our unit was 10.3±4.4 (range 0.7-17.9) years. Seventy-eight children were diagnosed with diabetes (new-onset group) during the study period. The median age of the new-onset group was 11.2 years (IQR:6.3-13.1) The distribution of, type 1 diabetes (T1D), type 2 diabetes (T2D), and monogenic diabetes was 79.5% (n=62), 7.7% (n=6), and 12.8% (n=10), sincerely. The distribution of the types was similar in the formerly diagnosed group and the new-onset group (p=0.899). Sixty-two cases (28 girls) with new-onset T1D were evaluated. The mean age was 9.3±4.6 years (range 0.7-17.9) and, twenty-one percent of them (n=13) were under 5 years of age. The rate of DKA at the presentation was 41.9%. Severe acidosis (pH<7.1) ratio was 19.4%, and the percentage of cases with HCO_3<5 mmol/L was 1.6%. Under 5 years of age, the ratio of acidosis and severe acidosis was higher than the cases older than 5 years (69.2% vs 34.7%, p=0.032 and 46.2% vs. 12.2%, p=0.013, sincerely).

Conclusion: In our study, the rate of monogenic diabetes was found to be higher. In the widespread use of high-throughput genetic techniques era, the diagnosis will change to monogenic diabetes in antibody-negative children followed up with the diagnosis of type 1 diabetes. The rate of DKA has remained unchanged for 40 year; this fact indicates that striking and continuous programs targeting increased awareness of diabetes are needed.

Keywords: Diabetes mellitus, type 1 diabetes, type 2 diabetes, MODY, diabetic ketoacidosis

ÖZ

Amaç: Bu çalışmada, çocuk endokrinoloji ünitesine iki yıllık dönemde başvuran diabetes mellitus (DM) tanılı pediatrik olguların bulgularının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Retrospektif, gözlemsel olarak planlanan çalışmada 0-18 yaş arası DM tanısı alan çocuk ve ergenler değerlendirildi. Olgular, önceden tanı almış ve yeni tanı olarak gruplandırıldı. Başvuru anındaki demografik ve laboratuvar özellikleri kaydedildi. Diyabet tipi ve diyabetik ketoasidoz (DKA) ve şiddetli DKA varlığı güncel kriterlere göre belirlendi.

Bulgular: Kliniğimizde değerlendirilen 108 çocuğun (51 kız) yaş ortalaması 10,3±4,4 yıl (aralık 0,7-17,9) idi. Olguların 78'ini çalışma döneminde tanı alan yeni tanı diyabetler oluşturdu. Yeni tanı diyabet olgularının ortanca yaşı 11,2 yıl idi (IQR:6,3-13,1). T1D, T2D ve monogenik diyabet dağılımı sırasıyla %79,5 (n=62), %7,7 (n=6) ve %12,8 (n=10). Diyabet tipi dağılımı önceden tanı almış grup ile yeni tanı alan grupta benzerdi (p=0,899). T1D'li 62 olgu (28 kız) değerlendirildi. Yaş ortalaması 9,3±4,6 yıl (aralık 0,7-17,9) idi. Beş yaşın altındaki olgu oranı %21 (n=13) idi. Başvuruda DKA oranı %41,9 idi. Şiddetli asidoz (pH<7,1) oranı %19,4, HCO_3<5 mmol/L olan olguların yüzdesi ise %1,6 idi. Beş yaş altında asidoz ve şiddetli asidoz oranı, beş yaş üstü olgulara göre daha yüksekti (sırasıyla %69,2 vs. %34,7, p=0,032; %46,2 ve %12,2, p=0,013).

Address for Correspondence: Saygın Abalı, Acıbadem Mehmet Ali Aydınlar University School of Medicine, Department of Pediatrics, Pediatric Endocrinology, İstanbul, Türkiye
Phone: +90 212 404 40 97 E-mail: saygin.abali@acibadem.edu.tr ORCID ID: orcid.org/0000-0001-6552-2801

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ÖZ

Sonuç: Bu çalışmada, monogenik diyabet oranı yüksek bulunmuştur. İleri genetik tekniklerin kullanılabilirliğinin artışı ile tip 1 diyabet tanısı ile izlenmekte olan antikor negatif olguların bazılarında monogenik diyabet tanısının konulabileceği düşünülmektedir. DKA oranının 40 yıldır değişmeden kalması, diyabet farkındalığını artırmaya yönelik çarpıcı ve sürekli programlara ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: Diabetes mellitus, tip 1 diyabet, tip 2 diyabet, MODY, diyabetik ketoasidoz

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic and multisystemic condition that occurs due to insulin deficiency and/or insufficiency in insulin action. American Diabetes Association (ADA) classifies DM as, type 1 diabetes (T1D) (usually absolute insulin deficiency due to autoimmune beta-cell destruction), type 2 diabetes (T2D) (non-autoimmune progressive loss of adequate insulin secretion frequently because of insulin resistance), specific types of diabetes due to other causes, and gestational diabetes mellitus. Specific types of diabetes include monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug -or chemical-induced diabetes and other causes (1).

The most common form of DM in children is T1D, and its incidence varies between countries (2). The number of new-onset and existing T1D cases is increasing (3). Worldwide, over 1.2 million children and adolescents younger than 20 years are estimated to have T1D. Approximately 150,000 children and adolescents under 20 years old are diagnosed each year (4). In Turkey, the total prevalence of T1D in children under 18 years was reported to be 0.75/1,000 (5), and 0.67/1,000 in school-age children (6-18 year old) in İstanbul (6). There are nearly 20,000 children under 18 years old with existing T1D in Turkey (7). The reported mean incidence in the last decade varies between 7.2-16.7 per 100,000 (5,8-10). These epidemiological studies showed that Turkey is a country with an intermediate incidence rate compared to the rest of the world (8). It is possible to say that there is an increase in the frequency of T1D in Turkey; however, since epidemiological data are scarce, it is based only on clinical observations and regional studies in the last decade. In regional studies during the 2010s from the eastern part of Turkey, an increase in the incidence of T1D was reported (9,10).

Acute complications are the most important cause of mortality and morbidity in children with T1D. Diabetic ketoacidosis (DKA), is one of the acute complications and is more frequent in new-onset cases who have risk factors such as young age, lower socioeconomic status, and living in a region with a low prevalence of T1D due to delayed diagnosis (11). The diagnosis of T1D may be delayed until the hospital admission for DKA, sometimes with fatal results. DKA frequency at diagnosis of T1D in high-income countries had been reported approximately 30% before 2020 (12). However, frequencies range from 15% to 70% in Europe and North America when the studies during the coronavirus disease-2019 (COVID-19) pandemic are included (13). Reducing the frequency of DKA and especially severe DKA in diagnosis is essential in terms of mortality, morbidity, and the emotional status of the families at the onset of diabetes. Activities targeting increased awareness of diabetes symptoms among parents, school teachers, and healthcare professionals have been successful in reducing DKA frequency (14,15).

T2D and other specific types of diabetes are also diagnosed during childhood. Adolescence is the period that T2D occurs in the pediatric age group, accounting for 15-86% of new-onset diabetic cases in adolescence in the United States (US). This variable rate is due to a disproportionally high incidence in some ethnic groups. In non-Hispanic white youth and in Europe, these rates are reported to be lower (16). In addition to the increase in obesity, many genetic/epigenetic mechanisms are thought to play a role in the development of T2D. Monogenic diabetes syndromes are diabetes due to single -gene alterations, including cases defined as maturity-onset diabetes of the young (MODY) as well as neonatal DM (NDM) cases diagnosed in the first 6 months of life. The frequency of monogenic diabetes in childhood diabetes is reported as 1%-6% (17).

This study evaluated the findings of pediatric cases with diabetes who were admitted to our Pediatric Endocrinology Unit in İstanbul between 01.04.2015 and 31.03.2017 for two years.

METHODS

In this retrospective, observational study, 108 (51 girls) children and adolescents aged 0-18 years, who applied to the Pediatric Endocrinology Unit in University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital in İstanbul between April 1st, 2015, and March 31st, 2017, and were diagnosed with DM according to the ADA criteria (1), were evaluated.

Thirty cases (14 girls) were diagnosed at another unit before April 1st, 2015, and admitted to our unit for follow-up. These cases were grouped as formerly diagnosed.

Seventy-eight (37 girls) were diagnosed in our unit during the study period and were grouped as new-onset.

Demographic (age, gender) and laboratory features [glucose (mg/dL), c-peptide level (ng/mL), presence of autoantibodies including islet cell autoantibodies (ICA), glutamic acid decarboxylase antibodies (GADA) and insulin autoantibodies (IA), presence of ketone bodies in urine, venous pH, and HCO_3 levels (mmol/L)] at admission were recorded.

The presence of DKA was described due to both International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 (venous pH<7.25 or HCO_3<15 mmol/L) (11) and ISPAD 2022 (venous pH<7.25 or HCO_3<18 mmol/L) (13). Severe DKA was defined as venous pH<7.1 or HCO_3<3 mmol/L.

The type of diabetes was evaluated, and cases were classified according to the ADA criteria (1).

T1D was diagnosed in insulin-deficient cases with the presence of autoantibody positivity, and the absence of any suggestive signs of other causes of diabetes. The diagnostic criteria for T2D were based on overweight/obesity, clinical findings of insulin resistance (acanthosis nigricans), family history of T2D, and good metabolic control with metformin or metformin combined with low-dose insulin. Children who had a family history of diabetes or specific findings such as deafness, optic atrophy, or renal cysts with negative autoantibodies and cases with an onset of diabetes younger than 6 months of age (NDM) were classified as clinically monogenic diabetes. The results of molecular genetic tests such as next-generation sequencing (NGS) that were performed on these cases were also recorded.

Statistical Analysis

Were performed using the statistical package for the social sciences software version 15 (LEAD Technologies Inc, 2006). Data were presented with n (%) for categorical data and mean ± standard deviation for numerical data. Chi-square tests were used for the comparison of categorical data (Fisher's exact test was used when chi-square test assumptions do not hold due to low expected cell counts). In the comparison of the independent 2 groups, the student t-test was used if the data were normally distributed, and the Mann-Whitney U test was used if the data were non-normally distributed. Type 1 error was determined as 5%, and a p-value <0.05 was considered statistically significant.

The study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (decision no: 2018-20/35, date: 20.12.2018). The study was retrospective and did not involve interventions; thus, informed consent from the parents and cases was not obtained. A consent waiver for this study was obtained from the ethics committee.

RESULTS

The mean age of 108 children (51 girls) at the time of the first evaluation in our unit was 10.3±4.4 (range 0.7-17.9) years. At diagnosis, 21.3% of the cases were younger than 5 years, and 55.6% of the cases were older than 10 years. Eighty-seven were diagnosed with T1D (80.6%), eight with T2D (7.4%), and 13 with monogenic diabetes (12.0%). The ratio of T2D in cases older than 10 years at diagnosis was 13.3%. The distribution of the cases are summarized in Figure 1.

Formerly Diagnosed Cases

Thirty children (14 girls) were diagnosed before the study period at another unit and admitted to our unit for follow-up. The median age of those at the onset of diabetes was 7.1 years ranging between 0.1 and 15.1 years The median duration of diabetes was 2.3 years. In this group, the distribution of T1D, T2D, and monogenic diabetes was 83.3% (n=25), 6.7% (n=2), and 10.0% (n=3), sincerely.

In the monogenic diabetes group, there was only one case (Case#91) with NDM, diagnosed on the postnatal 18th day. She had KCNJ11-NDM and had been switched to sulfonylurea (SU) (glibenclamide) in infancy, and was admitted first to our unit at the age of 4.1 years.

A case in this group, an 11-year-old girl (C#93), had been diagnosed with T1D at the age of 6 years. She had been treated with multiple daily injections (insulin lispro and glargine, total insulin 0.8 U/kg per day). GADA and ICA were negative. Her mother was also diagnosed with diabetes at the age of 14 years, the duration of her diabetes was 23 years, and she had severe microvascular complications such as retinopathy. There were many individuals with diabetes in their family; therefore, NGS panel for MODY was performed. In the *hepatocyte nuclear factor 1-α (HNF1A)* gene, a heterozygous frameshift variant (c.1853_1854delTC, p. Ile618Argfs*30) was detected both in C#93 and her mother. After the genetic diagnosis of HNF1A-MODY was established in these cases, transfer from insulin therapy to glibenclamide was attempted. In the girl, insulin requirement decreased, and insulin therapy ceased; however, the mother had no response to SU.

New-onset Cases

Seventy-eight children (37 girls) were diagnosed with diabetes in our unit during the study period. The median age of the new-onset group was 11.2 years (IQR25-75 6.3-

13.1) (mean age 9.9±4.4 years, range 0.7-17.9). In the new-onset group, the distribution of, T1D, T2D, and monogenic diabetes were 79.5% (n=62), 7.7% (n=6), and 12.8% (n=10), sincerely. The distribution of the types was similar in the formerly diagnosed group and the new-onset group (p=0.899).

Sixty-two cases (28 girls) with T1D were evaluated. The mean age was 9.3±4.6 (range 0.7-17.9). Twenty-one percent of them (n=13) were under 5 years of age. Only one case (C#74) was under 12 months of age. She was 8.7 months old at the onset of diabetes and had severe DKA, and three autoantibodies were positive.

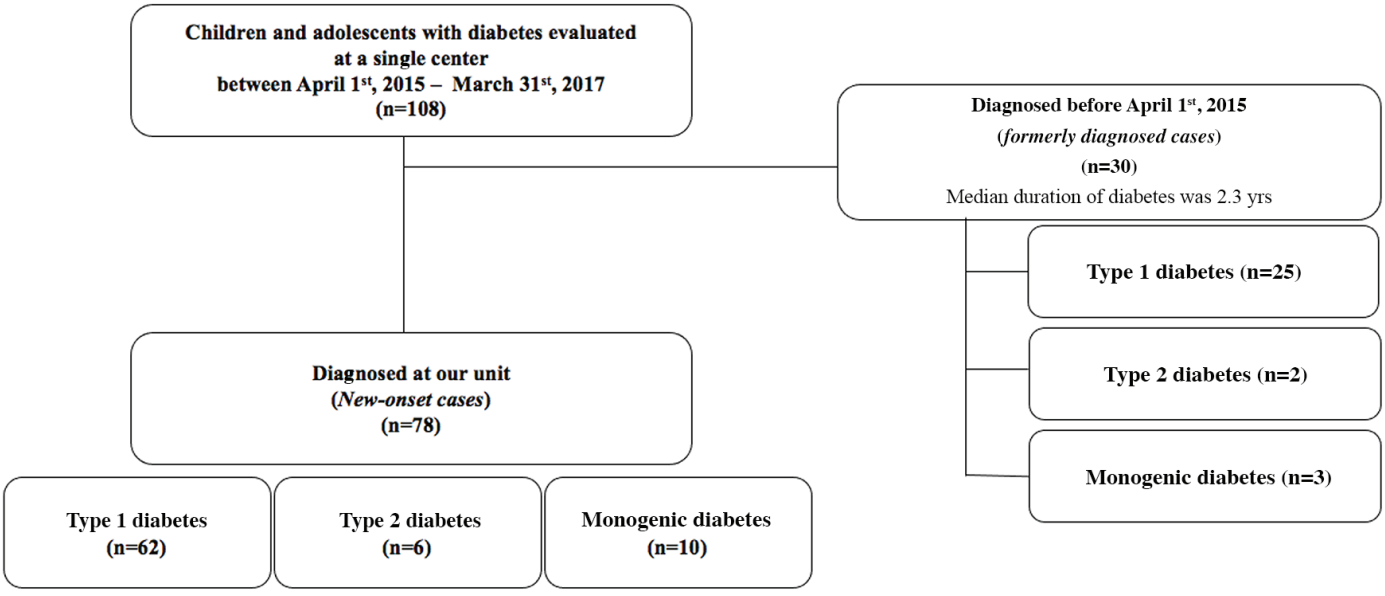

Figure 1. Distribution of cases according to the types of diabetes

Table 1. Features of children and adolescents with type 1 diabetes in the new-onset group

	Ketoacidosis (-)	Ketoacidosis (+)	All	p
Girls, n (%)	17 (42.3)	11 (47.2)	28 (45.2)	0.701
Age (years)	10.0±4.4	8.2±4.7	9.3±4.6	0.116
Age <5 years, n (%)	4 (11.1)	9 (34.6)	13 (21.0)	0.032
Glucose (mg/dL) mean ± SD	449.5±161.2	496.0±133.4	468.9±150.8	0.236
C-peptide (ng/mL) mean ± SD median	1.1±0.7 0.9	0.5±0.4 0.4	0.9±0.7 0.8	0.004
Ketonuria (+) n (%)	27 (75.0)	26 (100.0)	53 (85.5)	0.008
pH mean ± SD	7.37±0.05	7.11±0.11	7.26±0.15	<0.001
HCO_3 (mmol/L) mean ± SD	22.2±3.0	9.0±3.3	16.6±7.3	<0.001
GADA (+), n (%)	20 (62.5)	17 (68.0)	37 (64.9)	0.666
ICA (+), n (%)	21 (65.6)	20 (80.0)	41 (71.9)	0.231
IA (+), n (%)	4 (14.8)	6 (31.6)	10 (21.7)	0.277
Antibody (+), n (%)	25 (75.8)	24 (96.0)	49 (84.5)	0.064
Antibody (-), n (%)	7 (21.9)	1 (4.0)	8 (14.0)	0.067
Two or more antibodies (+), n (%)	19 (59.4)	15 (65.2)	34 (61.8)	0.660

GADA: Glutamic acid decarboxylase antibodies, ICA: Islet cell autoantibodies, IA: Insulin autoantibodies, SD: Standard deviation

The DKA-2018 (pH<7.30 or HCO_3<15.0 mmol/L) ratio at presentation was 41.9%. The percentage of cases with DKA-2022 (HCO_3<18 mmol/L) was 50.0%. Severe acidosis (pH<7.1) ratio was 19.4%, and the percentage of cases with HCO_3<5 mmol/L was 1.6%. Under 5 years of age, the ratio of acidosis and severe acidosis was higher than the cases older than 5 years (69.2% vs. 34.7%, p=0.032 and 46.2% vs. 12.2%, p=0.013, sincerely). Laboratory features of the cases with T1D are given in Table 1.

In 58 cases with T1D, at least one autoantibody level was tested. Seventy-nine percent of those had at least one positive antibody. Two or more antibodies were positive in 34 cases (54.8%). The ratio of cases with negative antibodies among the cases that were tested for at least two antibodies was 12.9% (n=8). A comparison between two-antibody-positive (n=34) and antibody-negative (n=8) cases in terms of median age, pH, and HCO_3 levels was performed. The median age, pH, and HCO_3 levels in these groups were 10.5 vs. 13.0 years (p=0.289), 7.30 vs. 7.39 (p=0.060), and 17.8 vs. 22.6 mmol/L (p=0.06), sincerely. The percentage of presence of urinary ketones was also similar in these groups (79.4% vs. 87.5%, p>0.05).

In the new-onset group, six cases (7.7%) were diagnosed with T2D. All of these cases were older than 10 years (range 10.4-15.3 years) and had body mass index (BMI) higher than 95 gentiles. No ketone body and no DKA were detected. All the three autoantibodies were negative in these cases. The frequency of T2D (n=6) among cases older than 10 years (n=47) was 12.8%.

Among the 10 cases with monogenic diabetes, seven cases were [Glucokinase (GCK)-MODY], and 5 of them had a result of a molecular genetic test compatible with the diagnosi; however, 2 of them only had a clinical diagnosis of GCK-MODY.

In the other monogenic diabetes cases (n=3), two cases (C#40 and C#47) with negative autoantibodies and with a strong family history, monogenic diabetes were clinically diagnosed. Unfortunately, molecular genetic tests in these cases could not be performed. The third case, a 14.8-year-old male adolescent (C#53), had a confirmed molecular diagnosis of [hepatocyte nuclear factor-1β (HNF1B)-MODY]. He had no known disease before and was admitted to our clinic with a complaint of polydipsia for a month. He was born at term with a weight of 2,750 g. There were no consanguinity and no family history of diabetes or kidney disease. His height and BMI standard deviation score were +1.0 and -0.7, sincerely. Systemic examination was normal, Tanner stage 5, and pectus excavatum was noticed. Serum glucose, urea, and creatinine were elevated (glucose 822 mg/dL, urea 62 mg/dL, and creatinine 1.49 mg/dL). Trace ketonuria without DKA was detected (venous pH 7.37 and HCO_3 26.7 mmol/L). Glycosylated hemoglobin (HbA1c) was 12.2%, and the c-peptide level was 0.87 ng/mL. Appropriate intravenous fluid and insulin therapy were initiated for severe hyperglycemia and high creatinine levels. Although euglycemia and normal hydration was achieved, a slightly elevated creatinine level persisted. Ultrasonography revealed increased echogenicity of the renal parenchyma and two cysts of 1 cm in diameter in the left kidney. An increase in the transaminase level was observed. GADA, ICA, and IA were found to be negative, and in the *HNF1B* gene c.827G>A, p. Arg276Gln, a missense heterozygous mutation was detected. His parents were negative for the variant.

All Cases

Overall, the ratio of monogenic diabetes was 12.8%. However, 6 (7.7%) of them had confirmed molecular etiology. The ratio of monogenic diabetes by excluding GCK-MODY cases and was found to be 4.3%.

Apart from these cases of monogenic diabetes, in our cohort, there were 8 cases with negative autoantibodies. In six of them with a classical presentation, without obesity, and without a negative family history, the T1D diagnosis was almost determined. However, in 2 cases with three negative autoantibodies, the type of DM could not be determined. In C#40, a 14.5-year-old girl, presenting with obesity, and trace ketonuria, without DKA, had an HbA1c level of 14.4%. She had a strong family histor; however, no variant was detected in the MODY gene panel with NGS. In C#59, a 14.9-year-old girl with obesity had intellectual insufficiency and she presented without DKA. A c-peptide level of 2.49 ng/mL was found, while her glucose level was 274 mg/dL.

All cases with monogenic diabetes in the formerly diagnosed and new-onset groups are given in Table 2.

DISCUSSION

In this study, we presented our pediatric diabetes cohort from a newly established center in İstanbul. There are many similar studies from Turkey (18,19); however, most of them are either from tertiary centers in high-populated provinces or from centers in relatively-low-populated provinces. This study differs from previous studies since it is from a non-tertiary center in a high-populated province. Additionally, we think that it is necessary to continue these audit studies in terms of the trends in the changing characteristics of children with diabetes.

Table 2. Clinical and genomic features of cases with monogenic diabetes

# Case	Age at diagnosis, gender	Family members with diabetes	Glucose mg/dL, ketone	HbA1c (%)	Acidosis	Ab	Gene	Variant zygosity
27	11.0, M	Sister (C#30), father, uncle, grandfather	142, negative	6.6	-	+ GADA	*GCK*	c.46-2A>G heterozygous
30	15.1, F	Brother (C#27), father, uncle grandfather	129, negative	6.7	-	-	*GCK*	c.46-2A>G heterozygous
40	15.2, F	Sister, mother, grandmother	343, positive	15.9	-	-	*N/A*	-
47	12.4, F	Father, grandmother	229, negative	11.5	-	-	*N/A*	-
53	14.8, M	No family history of diabetes	822, trace	12.2	-	-	*HNF1B*	c.827G>A p.Arg276Gln heterozygous
55	11,4, F	Brother, mother, aunt	131, negative	6.1	-	-	*GCK*	c.1226A>C p.Asp409Ala heterozygous
58	11.6, M	Father, grandfather	142, negative	N/A	-	-	*GCK?*	N/A
60	13.4, F	Mother, grandfather	126, negative	N/A	-	-	*GCK?*	N/A
70	5.1, M	Father	127, negative	N/A	-	-	*GCK*	c.1256G>C p.Arg422Pro heterozygous
72	11.3, F	N/A	130, negative	6.6	-	-	*GCK*	c.227C>T p.Ser76Phe heterozygous
91	0.1, F	No family history of diabetes	N/A	N/A	N/A	N/A	*KCNJ11*	c.155A>T p.Gln52Leu heterozygous
93	6.0, F	Mother, aunts, uncles	170, negative	6.7	-	-	*HNF1A*	c.1853_1854delTC p.Ile618Argfs*30 heterozygous
97	14.5, M	No family history of diabetes	519, negative	14.6	-	-	*WFS1*	c.2206G>A p.Gly736Ser homozygous

F: Female, M: Male, *HNF1A: Hepatocyte nuclear factor 1-α, GCK: Glucokinase, HNF1B: Hepatocyte nuclear factor-1β*

The distribution of types of DM differs due to many factors. In Caucasians, T1D constitutes by far the majority (over 90%) of childhood diabetes (2). Overall in our cohort, the T1D ratio was 80.6%. Although similar to previous studies, T1D is the most common, the percentage is lower. Considering that there may be a bias regarding the application of formerly diagnosed patients, this rate was also evaluated in cases diagnosed in the study period at our center (new-onset cases) and a similar result was found (79.5%). As can be seen, 1/5 of the cases were not T1D. The reason for this high rate of non-T1D cases is explained by the high frequency of monogenic diabetes (approximately 12.8%) in our cohort, which is commonly reported in different studies as 1%-6% of childhood diabetes (17). There are two considerable factors in determining this high rate in our cohort. The first one may be that possible cases without molecular genetic confirmation were also included in the monogenic diabetes group. The ratio was 7.7% if only cases with confirmed molecular etiology were included. However, we believe that the cases without detectable variants would be confirmed with the increased availability of high-throughput genetic testing such as whole-exome sequencing. For this reason, we think that the accepted rates (1%-6%) for monogenic diabetes belong to the periods when the accessibility

of molecular genetic tests was insufficient. Today, the main criteria for genetic testing in diabetes are negative-autoantibodies and having a strong family history (1). Because of the autosomal dominant inheritance pattern of the disease, antibody-negative atypical cases without a family history should also be included in genetic testing due to possible *de novo* variants as we detected in our case with HNF1B-MODY. Apart from these cases that we determined to have monogenic diabetes in our cohort, there were eight more cases with negative autoantibodies. In six of them with a classical presentation, without obesity, and without a negative family history, the T1D diagnosis was almost determined. However, in two cases with three negative autoantibodies, the type of DM could not be determined. In a recent study from Finland (20), more than 10% of antibody-negative children with diabetes were found to be a genetic variant and diagnosed with monogenic diabetes regardless of the family history of diabetes. We believe that, as high-throughput genetic tests become easily available, the rate of monogenic diabetes in children will reach over 10%, at least in countries with an intermediate incidence of T1D.

The second factor for the high rate of monogenic diabetes would be the low threshold for testing the GCK variants in mild fasting hyperglycemia. GCK-MODY presents with a different clinical picture from typical childhood diabetes, and in many cohorts, mild cases would not be included. Therefore, we calculated the rate of monogenic diabetes in our cohort also by excluding GCK-MODY cases and found it to be 4.3%. Recent publications have reported that GCK-MODY is the most common type of monogenic diabetes (21,22). Detecting pathogenic *GCK* gene variants in cases with fasting hyperglycemia would prevent unnecessary treatment in cases misdiagnosed with T2D (1,17). Additionally, some of these cases with GCK-MODY are being followed closely with the diagnosis of prediabetes, and this could be over.

The most important consequences of determining of the diagnosis of monogenic diabetes are genetic counseling and detection of other accompanying conditions, as in our case with HNF1B-MODY. Additionally, as in the cases of HNF1A-MODY, and KCNJ11-NDM in our cohort, the chance of change in treatment is very striking in childhood diabetes.

The frequency of childhood T2D has increased dramatically in North America, especially in ethnic minority populations (23). While the frequency of T2D in children is increasing in the US (24), this ratio is still lower in Europe (1.3%) (25). In a single-center study in İstanbul (18), it was reported that 5.7% of childhood diabetes diagnosed between 1999 and 2016 and 11.8% of children older than 10 years were T2D. It was also shown that there was a significant increase in the frequency of T2D among all DM between 2011 and 2016 compared to previous years. The rate of T2D in children over the age of 10 between 2011 and 2016 was 16% (18). In our cohort, 7.7% of the cases were diagnosed with T2D. All of these cases had obesity, and all were older than 10 years. The frequency of T2D among cases older than 10 years was 12.8%. No ketone body and no DKA were detected. All three autoantibodies were negative in cases with T2D in our cohort. T1D and T2D are heterogeneous disorders, and some cases cannot be clearly classified at the onset of DM (1). In our cohort, cases with their typical features were easily diagnosed with T2D. Although the positive autoantibodies are mostly related to T1D, up to 15% of the cases with T2D had positive autoantibodies (18,26). Also, cases with T2D may rarely present with DKA, and the expected glucose levels at presentation are mostly lower than the cases with T1D (<360 mg/dL) (1,27).

Immune-mediated diabetes diagnosed with autoantibodies include ICA, GADA, IA, and tyrosine phosphatases islet antigen 2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8) are important in the classification of diabetes in children. In our cohort, 58 cases with T1D, at least one autoantibody level was tested. One of the clinical limitations in our routine practice is that IA-2, IA-2b, and ZnT8 antibodies cannot be tested. Seventy-nine percent of those had at least one positive antibody. Two or more antibodies were positive in 54.8%. The ratio of cases with negative antibodies among the cases that were tested for at least two antibodies was 12.9%.

The second outcome of our study is the DKA frequency in T1D. DKA is the foremost morbidity and mortality cause of T1D. The frequency of the DKA in our new-onset T1D cohort was presented both due to ISPAD-2018 (11) and ISPAD-2022 (13), 41.9% and 50.0%, sincerely. The severe acidosis (pH<7.1) ratio was 19.4%. However, mostly we used HCO_3<5 mmol/L criteria for the definition of severe acidosis in our clinical practice, and the ratio of these cases was 1.6%.

Recently, a comprehensive review of the DKA rate in children with T1D covering almost all studies from Turkey over 40 years by Esen and Okdemir (19) was published. The rate of DKA at the onset of DM was reported as 45.6% in 8837 children. The limitations of this review were that the designs of the studies included in this review were heterogeneous and that only the abstracts of some studies have been evaluated. As seen in this review, apart from the periodical and regional small differences between the studies, by 2019, there was no change in the rate of DKA in Turkey for the last 40 years (19). In our cohort, the frequency of DKA at the onset of DM was similar.

Programs targeting increased awareness of diabetes symptoms among parents, school teachers, and, healthcare professionals have been successful in reducing DKA frequency (14,15). In Turkey by the 2010s, childhood diabetes program activities (7,28) have been carried out. Although a positive effect of these programs on the DKA rate at the onset of DM was reported in a study (29), it is seen that this study had showed an acute effect of the program since it was carried out in the next year of the program. This effect was not demonstrated by later studies (19) due to the limited memory of the community in the long term. Awareness again decreased and the frequency increased to similar levels. It would be beneficial to conduct continuous programs, especially to reduce severe acidosis.

In our cohort, in young cases (<5 years), DKA and severe DKA rates were significantly found to be higher. The risk of DKA at the onset of T1D is greater in younger children due to the difficulty in recognizing the symptoms of diabetes. While in some studies, no difference was reported in DKA rate due to age groups, some studies as our cohort found that the frequency of DKA was higher in children (19). A relationship between DKA risk and being younger than 5 years was shown by Uçar et al. (29).

In our cohort, no gender difference was found between cases presented with DKA and without DKA during the onset of T1D. The effect of gender on the DKA rate was evaluated in a meta-analysis (30), and no effect was detected. In Turkey, studies reported different DKA rates in terms of gender. In the two largest cohorts evaluating the long-term experience of centers, DKA rates at the onset of T1D were reported to be higher in girls (31,32). In subsequent studies, it was observed that there was no gender difference (19).

After COVID-19, increased rates of DKA at the onset of T1D were reported from six centers in Turkey. These six studies all together showed that while the DKA rate 42.3% in the 2018-2020 period before COVID-19, it was increased to 59.3% between 2020 and 2022 during the COVID-19 period (33-38). The reasons for the increase were attributed to the decrease in the awareness of other diseases due to the severe COVID-19 clinic and delays in admission to the hospital.

CONCLUSION

The rate of monogenic diabetes was found to be higher in our study. In the widespread use of high-throughput genetic techniques era, the diagnosis will change to monogenic diabetes in antibody-negative children followed up with the diagnosis of T1D. The rate of DKA has remained unchanged for 40 year; this fact indicates that striking and continuous programs targeting increased awareness of diabetes are needed.

ETHICS

Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (decision no: 2018-20/35, date: 20.12.2018).

Informed Consent: The study was retrospective and did not involve interventions; thus, informed consent from the parents and cases was not obtained.

Authorship Contributions

Surgical and Medical Practices: S.A., Y.A., Concept: S.A., Design: S.A., Data Collection or Processing: S.A., Y.A., Analysis or Interpretation: S.A., Literature Search: S.A., Writing: S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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