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Change in clinical presentation at admission in children with newly diagnosed type 1 diabetes during the COVID-19 pandemic in the eastern region of Turkey

Ismail Dundar[a,*], Aysehan Akinci[a], Emine Camtosun[a], Nurdan Ciftci[a], Leman Kayas[a]

[a] *Inonu University, Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Türkiye*

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Abstract

Aim: The COVID-19 pandemic is a global health problem with high morbidity and mortality. This study aimed to compare the clinical features of newly diagnosed type 1 diabetes (T1D) patients during the pandemic with those diagnosed earlier and evaluate how the pandemic affected the T1D clinical findings on admission.

Materials and Methods: This is a 2-year, single-center, cross-sectional study. The time between March 11, 2019, and March 11, 2020, was defined as the "pre-pandemic period," while the interval between March 11, 2020, and March 11, 2021, was called the "pandemic period." The clinical and laboratory parameters of newly diagnosed T1D patients admitted in these two time periods were compared.

Results: The admission rate with DKA was higher in the pandemic period than in the pre-pandemic time (71.0% and 52.8%, respectively, p=0.046). There was no difference between the groups regarding the severity of DKA. The mean duration of diabetes symptoms before diagnosis was longer during the pandemic than in the pre-pandemic period (17.0 days and 12.5 days, respectively, p=0.035).

Conclusion: Delayed admissions to health institutions of patients with diabetes signs and symptoms during the pandemic are worrisome. This delay is likely to have increased the DKA rate during the pandemic. As a result, children with diabetes symptoms should be ensured to apply to a health institution without hesitation, even in the pandemic.

Introduction

The World Health Organization (WHO) announced the Coronavirus Disease 2019 (COVID-19), which has turned into a global health problem and caused high morbidity and mortality shortly, as a pandemic on March 24, 2020 [1,2]. The first COVID-19 case in Turkey was seen on March 11, 2020, in Istanbul [3].

SARS-CoV-2 is an RNA virus belonging to the β variant of the coronavirus family [4]. Clinical manifestations of COVID-19 caused by SARS-CoV-2 are age-related [5]. Adults develop respiratory symptoms that can progress to acute respiratory distress syndrome (ARDS) in the most severe form, while children are largely spared from respiratory disease but may develop a life-threatening multisystem inflammatory syndrome (MIS-C) [6]. The COVID-19 disease not only directly affects children's health but also affects them socially, biologically, and economically. Limited studies report interesting findings on the increase in the prevalence of newly diagnosed type 1 diabetes (T1D) during the COVID-19 pandemic and the clinical severity of patients' symptoms at the first admission [7-10].

In this study, the effect of the COVID-19 pandemic on the clinical presentation of patients with newly diagnosed T1D was investigated by comparing it with the pre-pandemic periods.

Materials and Methods

Patients under 18 who were recently diagnosed as T1D in the Pediatric Endocrinology clinic of Inonu University, Medical Faculty Hospital between March 11, 2019, and March 11, 2021, were included in this study. One year after March 11, 2020, when the first case of COVID-19 was seen in Turkey (March 11, 2020 - March 11, 2021), was defined as the "pandemic period," and the year before this date (March 11, 2019 - March 11, 2020) was called the "pre-pandemic period." Since there is only one pediatric endocrinology center in Malatya, we evaluated the data of all newly diagnosed T1D patients in the city. Our hospital serves as a reference hospital in the East and South-

*Corresponding author:
Email address: ismail_dundar@yahoo.com (Ismail Dundar)

east regions of Turkey. Malatya is one of the big cities of Turkey. Additionally, Syrian refugees residing in this region were included in the study. Exclusion criteria were cases with syndromic diabetes, Type 2 diabetes (T2D), maturity-onset diabetes of youth (MODY), and secondary causes of diabetes, such as cystic fibrosis, steroid use, and lipodystrophy.

We determined the diagnosis of T1D according to the 2018 criteria of the International Pediatric and Adolescent Diabetes Association [11]. Diabetic ketoacidosis (DKA) was defined as hyperglycemia (PG $\geq$ 200 mg/dL) with acidosis (venous blood pH $<$ 7.30 and/or serum bicarbonate $<$ 15 mmol/L), ketonemia, and/or ketonuria. The clinical presentation was classified into three groups: 1) hyperglycemia only (without ketosis or acidosis), 2) hyperglycemia with ketosis (without acidosis), and 3) ketoacidosis (DKA). For the purposes of this study, a ketosis assessment was performed by measuring urinary ketone semiquantitatively. Thus, ketonuria was present when urinary ketones were $\geq$2+. Urinary ketone measurements were performed by an automated analyzer, which used sodium nitroprusside reaction as the test principle (BT URICELL 1280-1600 devices, BT products, İzmir, Turkey) in each voiding. Patients diagnosed with diabetes during the pandemic were searched for a SARS-CoV-2 infection using a positive real-time polymerase chain reaction (RT-PCR) test results from nasopharyngeal and oropharyngeal samples [12].

The DKA severity was classified according to the Lawson Wilkins Pediatric Endocrine Society Consensus Statement (13): severe DKA (venous pH $<$7.10, serum bicarbonate $<$5 mmol/L), moderate DKA (venous pH 7.10 – 7.19, serum bicarbonate between 5 and 10 mmol/L), and mild DKA (venous pH 7.20 – 7.29, serum bicarbonate between 10 - 15 mmol/L). In addition, demographic and clinical features at the time of diagnosis, including sex, birth date, diagnosis date, the season of admission, duration of symptoms before diagnosis, and the type of presentation (DKA, hyperglycemia with ketosis, or hyperglycemia only) were collected. Furthermore, laboratory results, including venous blood glucose concentration, c-peptide concentration, hemoglobin A1c (HbA1c) percentage, and the presence of T1D-associated autoantibodies, such as anti-glutamic acid decarboxylase antibodies (GAD), insulin antibodies (IAA), and islet cell antibodies (ICA) were obtained from patient files. ICA, IAA, and GAD levels were measured using enzyme-linked immunosorbent assays based on antigen-antibody detection with the Isletest commercial kit using the Seac Brio 410499 model instrument. The HbA1C level was studied with the Agilent 1100 HPLC analyzer (Agilent Technologies, Waldbronn, Germany) available in our hospital.

Ethics approval was obtained for the study from the Ethics Committee of İnönü University Faculty of Medicine (date: 04/05/2021; IRB number: 2021/1956).

Statistical analysis

Data were presented as mean ± standard deviations (SD). Data analysis was performed using the SPSS for Windows statistical software (version 17.0; SPSS, Chicago, IL, USA). The student's two-tailed t-test was used for comparisons between independent variables with a normal distribution. Mann-Whitney U-test was used for the comparison of variables with skewed distribution. Comparisons were made by crosstabulation and Chi-square statistics. A p-value of $<$ 0.05 was considered statistically significant.

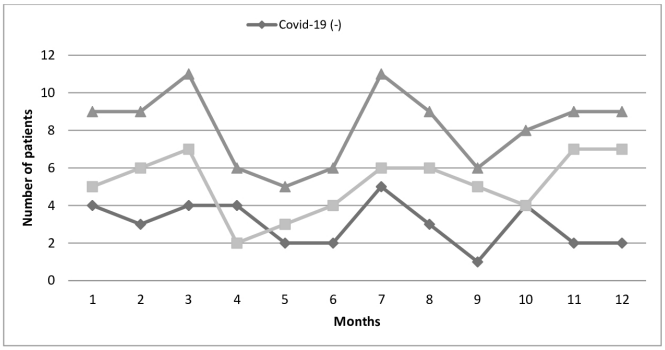

Figure 1. Distribution of age of onset of type 1 diabetes according to months of the year.

Results

The cohort consisted of 98 patients (<18 years old). Forty-six were females (46.9%), and fifty-two were males (53.1%). The mean age at diagnosis was 9.1±4.3 years, with a range of 1.1-17.9 years. Demographic, clinical, and laboratory characteristics of our patients are shown in Table I.

The months of diagnosis of T1D are given in Figure I. Serum autoantibody levels of all cases were evaluated. GAD (71.40%) was the most common, followed by ICA (63.3%) and IAA (37.8%). Although at least one of the three antibodies was positive in 80 (81.6%) of the patients, none of the three antibodies was detected in 18 (18.4%) children. The frequency of ICA detection increased from 19.8% in the pre-pandemic period to 48.4% during the pandemic (p=0.005) (Table II).

The clinical picture was evaluated at the time of diagnosis in all cases (36 patients in pre-pandemic and 62 patients in pandemic period). During the pandemic, the COVID-19 PCR test was positive in six of the patients. One patient was diagnosed with COVID-19 two months before the T1D, one case one month before, and four patients during the diagnosis. Two of our COVID-19 patients admitted with ketosis, and four patients with DKA. Furthermore, three of our COVID-19 patients admitted with DKA applied with moderate DKA and one with severe DKA.

Key features of the presentation were compared between pre-pandemic and pandemic periods. The frequency of admission with DKA increased during the COVID-19 period Table II. The frequency of DKA subgroups did not change between the time intervals. The duration of diabetes symptoms before diagnosis was longer during the pandemic than in the pre-pandemic period (17.0 days and 12.5 days, respectively, p=0.035).

Discussion

T1D is one of the most important chronic diseases of childhood. Its incidence in Turkey is among the countries with

Table 1. Demographic, clinical and laboratory characteristics of type 1 diabetes patients at the time of diagnosis according to age groups.

Age group		0-4 yaş	5-9 yaş	10-13 yaş	14-18 yaş	Total (0-18)
Number of patients						
	• Female n, (%)	11 (64.7)	17 (58.6)	12 (32.4)	6 (40)	46 (46.9)
	• Male n, (%)	6 (35.3)	12 (41.3)	25 (67.6)	9 (60)	52 (53.1)
	• Total n, (%)	17 (17.3)	29 (29.6)	37 (37.8)	15 (15.3)	98 (100)
Puberte						
	• Prepubertal	17 (100)	29 (100)	16 (43.2)	0 (0)	62 (63.3)
	• Pubertal	0 (0)	0 (0)	21 (56.7)	15 (100)	36 (36.7)
Diabetes diagnosis age		2.1 ± 1.0	7.1 ± 1.4	11.4 ± 1.5	15.3 ± 1.0	9.1 ± 4.3
Family history of diabetes , %		17.6	17.2	10.8	13.3	14.3
Duration of symptoms before diagnosis (days)		14.2 ± 9.2	14.5 ± 8.3	16.1 ± 11.5	16.6 ± 10.5	15.3 ± 8.9
Glucose (mg/dL)		534 ± 160	560 ± 160	516 ± 130	508 ± 156	531.3 ± 148
C-peptide (ng/mL)		0.30 ± 0.26	0.44 ± 0.24	0.51 ± 0.44	0.55 ± 0.47	0.49 ± 0.37
HbA1c (%)		10.4 ± 1.9	11.8 ± 1.4	12.3 ± 1.5	13.2 ± 3.0	12.0 ± 2.0
Anti-GAD positivity n, (%)		12 (70.6)	21 (72.4)	26 (70.3)	11 (73.3)	70 (71.4)
ICA positivity n, (%)		11 (64.7)	19 (65.5)	23 (62.2)	9 (60.0)	62 (63.3)
IAA positivity n, (%)		9 (52.9)	11 (37.9)	13 (35.1)	4 (26.7)	37 (37.8)
Main presenting feature						
	• Hyperglycemia n, (%)	2 (11.8)	4 (13.8)	3 (8.1)	1 (6.7)	10 (10.2)
	• Ketosis n, (%)	4 (23.5)	9 (31.0)	8 (21.6)	4 (26.7)	25 (25.5)
	• Ketoacidosis n, (%)	11 (64.7)	16 (55.2)	26 (70.3)	10 (66.7)	63 (64.3)
Severity of DKA						
	• Mild DKA n, (%)	2 (18.2)	6 (37.5)	6 (23.1)	1 (10.0)	15 (23.8)
	• Moderate DKA n, (%)	2 (18.2)	4 (25.0)	11 (42.3)	6 (60.0)	23 (36.5)
	• Severe DKA n, (%)	7 (63.7)	6 (37.5)	9 (34.6)	3 (30.0)	25(39.7)
Hospital stay time (days)		12.2 ± 2.2	10.8 ± 2.1	10.6 ± 2.9	10.4 ± 1.6	10.9 ± 2.5

GAD: Glutamic acid decarboxylase antibody, IAA: Insulin antibody, ICA: Islet cell antibody, HbA1C: Hemoglobin A1c.

an intermediate level [14]. DKA is the leading cause of morbidity and mortality in children with T1D, and the occurrence of DKA at the time of diagnosis is associated with long-term poor metabolic control [15,16]. T1D is a multifactorial disease. In addition to being exposed to environmental factors such as foods, toxins, chemicals, and infectious agents (especially viruses) at an early age, individuals with a genetic predisposition are also affected by physical and psychosocial stress [17,18,19]. The incidence of T1D increases after physical hazards such as earthquakes and nuclear accidents, which have national and international effects and are classified as social stress factors [20,21].

Similarly, the restriction of social interaction between children and adolescents due to the pandemic and the prolongation of this process can be considered psychosocial stress factors [22]. It has been observed that physical and environmental stress factors increase inflammatory T cell-mediated beta-cell damage in rats, causing oxidative stress and an increase in proinflammatory cytokines [23]. That coronavirus, an RNA virus, has been accused of causing pancreatic beta-cell damage [24].

High rates of T1D patients were admitted to hospitals with DKA before the COVID-19 pandemic. In a multicenter report including data from the USA, Europe, and Australia, the presentation rates of T1D patients with DKA vary between 19% and 43.8% [25]. In Turkey, the rate of DKA in T1D presentation is very high in children [14,26,27]. A study conducted in Italy reported a dramatic decrease in DKA presentation from 78% to 12.5% as a result of a public health campaign targeting teachers, students, and pediatricians [28]. Similarly, after a two-year diabetes awareness campaign in Australia focused on childcare centers, schools, and doctor's offices, children presenting with DKA decreased from 37.5% to 13.8% [29]. In light of these studies, we think that similar successful programs aiming to reduce DKA frequency in children with T1D are needed in Turkey.

Since the onset of the COVID-19 pandemic in Turkey, an increase in the presentation of DKA has been observed in children with newly diagnosed T1D. Studies conducted in the USA, Europe, and Canada report an increase in the severity of DKA along with the rate of DKA [8,30,31,32]. However, studies showing the opposite have been reported. In a survey from Australia, no increase in DKA frequency was found during the COVID-19 pandemic [33]. In our study, while the frequency of DKA increased from 52.8% to 71.0% during the COVID-19 pandemic, no significant change was found in the severity of DKA. During the pandemic in Germany, admission with DKA in patients with T1D increased from 23.5% to 44.7%, and there was an increase in severe DKA from 13.9% to 19.7% [30]. Also,

Table 2. Comparison of clinical and laboratory findings before and during COVID-19 period in patients with T1D.

		Period 1 (15 Mart 2019 - 15 Mart 2020)	Period 2 (15 Mart 2020 - 15 Mart 2021)	p value
Number of the patients		36	62	
Age (years)		8.8 ± 4.0	9.3 ± 4.5	NS
Gender n, (%)				
	• Female	18, (50)	28, (45.2)	
	• Male	18, (50)	34, (54.8)	NS
Age Groups				
	• Ages of 0-4 n, (%)	5, (13.9)	12, (19.4)	NS
	• Ages of 5-9 n, (%)	14, (38.9)	15, (24.2)	NS
	• Ages of 10-13 n, (%)	11, (30.6)	26, (41.9)	NS
	• Ages of 14-18 n, (%)	6, (16.7)	9, (14.5)	NS
Duration of symptoms before diagnosis (days)		12.5 ± 5.8	17.0 ± 9.9	0.035
Glucose (mg/dL)		533 ± 142	530 ± 152	NS
C-peptide (ng/mL)		0.45±0.3	0.46 ± 0.4	NS
HgA1C (%)		12.0 ± 1,6	12.0 ± 2.2	NS
Main presenting feature				
	• Hyperglycemia n, (%)	4 (11.1)	6 (9.7)	NS
	• Ketosis n, (%)	13 (36.1)	12 (19.4)	0.038
	• Ketoacidosis n, (%)	19 (52.8)	44 (71.0)	0.046
DKA n, (%)				
	• Mild DKA	4, (21.1)	11, (25)	NS
	• Moderate DKA	7, (36.8)	16, (36.4)	NS
	• Severe DKA	8, (42.1)	17, (38.6)	NS
Anti-GAD positivity n, (%)		22, (61.1)	48, (77.4)	NS
ICA positivity n, (%)		7, (19.8)	30, (48.4)	0.005
IAA positivity n, (%)		26, (72.2)	36, (58.1)	NS
Hospital stay time (days)		11.02 ± 2.7	10.8 ± 2.3	NS

GAD: Glutamic acid decarboxylase antibody, IAA: Insulin antibody, ICA: Islet cell antibody, HgA1C: Glycolize hemoglobin. NS: Not significant.

data from Italy show an increase in severe DKA from 36% to 44.3% during the COVID-19 pandemic [8]. Similar increases were reported in data from Canada [31]. Our rates of admission with pre-pandemic DKA were high, but it was observed that the rise in DKA frequency became more evident with the pandemic; however, no difference was observed in the severity of DKA. According to our results, the potential negative impact of the COVID-19 pandemic on the health of children with T1D raises concerns. Given the importance of social isolation during the pandemic, families are likely to hesitate to seek medical help. The lack of transition to virtual medical visits in our province is also expected to have contributed to the increase in DKA. DKA is managed in intensive care settings, and therefore, the increased need for intensive care due to covid-19 during the pandemic had probably adverse effects on the appropriate intensive care of DKA due to T1D. Studies have reported that families hesitate to admit their patients to emergency services and health institutions during the COVID-19 pandemic [8,34]. In our research, while the mean duration of symptoms before diagnosis was 12.5 days before COVID-19, this duration was 17.0 days in the COVID-19 period. There has been a delay in hospital admissions due to fear of contamination and regulatory changes of hospitals. This delay resulted in an increased incidence of DKA and poor metabolic control.

The physiopathology of the systemic effects of COVID-19 is thought to be similar to autoimmune diseases due to T-lymphocyte dysfunctions and increased inflammatory cytokine effects [35]. On the other hand, autoantibodies, biomarkers of autoimmune diseases, can also be detected in COVID-19 patients (36). Studies have identified COVID-19 as a risk factor for autoimmune disease [36,37]. In their research, Dilek et al. found that ICA positivity and Anti-GAD positivity increased during the COVID-19 pandemic compared to earlier [10]. Our study found a non-significant increase in Anti-GAD positivity and a statistically insignificant decrease in IAA positivity during the pandemic. However, a significant increase was found in ICA positivity. It has been shown that the Coxsackie B4 virus has a similar homology with anti-GAD and induces autoimmune pancreatic beta-cell damage [38]. Although there is not enough information about the diabetogenic effects of COVID-19 and its impact on post-infection diabetes, it is thought that similar autoimmune damage may occur in COVID-19 infection. The COVID-19 virus enters

cells through ACE2 and TMPRSS2 receptors in pancreatic ducts and microvascular structures, but these receptors have not been detected in beta cells so far. Therefore, it refuted the hypothesis that COVID-19 could directly infect pancreatic beta cells [39]. In our study, COVID-19 PCR was positive in four of our patients during the diagnosis of T1D, and hyperglycemia persisted despite COVID-19 becoming negative. This supports the hypothesis that COVID-19 does not directly infect beta cells. Although it is thought that a possible autoimmune damage mechanism might have been triggered in one of our cases with a history of COVID-19 two months before the diagnosis and in one of our cases one month ago, this situation does not seem likely due to the long process of T1D.

Our findings highlight the importance of encouraging hesitant families to bring their children to health care facilities. Awareness of the symptoms of hyperglycemia (polyuria, polydipsia, nocturia, enuresis, and weight loss) is essential, both among the public and healthcare providers. The importance of immediate referrals to the emergency departments or pediatric diabetes clinics should be emphasized. As healthcare providers, we must also strive to reduce barriers to families' access to appropriate care. Finally, we must systematically monitor the potential effects of the COVID-19 pandemic on children with diabetes over longer terms and develop new strategies.

Conclusion

Higher rates of DKA were found in patients who applied to our center with newly diagnosed T1D during the COVID-19 pandemic. As a result, there is a need for information and education campaigns to prevent delayed admissions of children with diabetic symptoms.

Ethics approval

Ethics approval was obtained for the study from the Ethics Committee of Inonu University Faculty of Medicine (date: 04/05/2021; IRB number: 2021/1956).

Patient consent

In this retrospective study, data were obtained from file records and consent was not obtained from patients.

Peer review

By the editorial board and peers outside the editorial board.

Conflict of interest

No conflict of interest was reported by the authors.

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