**Anastasiya N. Lazareva1, Alexey Yu. Rtishchev2,3, Irina G. Vorontsova3, Irina G. Rybkina2, Elena E. Petryaykina2,3**

1 Children's City Outpatients Clinic №122, Moscow, Russian Federation

2 Morozovskaya Children's City Hospital, Moscow, Russian Federation

3 Pirogov Russian National Research Medical University, Moscow, Russian Federation

**Type 1 Diabetes Onset in Children after COVID-19: Cross-Sectional Study**

**Contact information**

Petryaykina Elena Efimovna, doctor of medicine, head of endocrinology department of Maternity and childhood institute in Pirogov Russian National Research Medical University, pediatric endocrinologist of endocrinology department in Morozovskaya Children's City Hospital.

**Address**: 117997, Moscow, Ostrovityanova street, 1**.**, e-mail: lepet\_morozko@mail.ru.

**Background.** The hypothesis on correlation between SARS-CoV-2 infection and diabetic ketoacidosis (DKA) development in patients with newly diagnosed type 1 diabetes (T1D) was proposed during the COVID-19 pandemic. The results of testing this hypothesis remain contradictory.

**Objective. Aim of the study** **—** to analyse the correlation between COVID-19 and clinical characteristics of T1D onset in children.

**Methods.** The study included data from the medical records of patients with newly diagnosed T1D and hospitalized from March 2020 to March 2021. The study group included patients with IgG to SARS-CoV-2 ≥10 U/ml at hospital admission, control group — patients with no laboratory signs of COVID-19. Clinical forms of disease manifestation (hyperglycemia, ketosis, DKA) were recorded among T1D features, as well as DKA severity according to blood pH levels (mild — pH≥7.3; moderate — pH=7.1-7.2; severe — pH<7.1).

**Results.** The study group included data from 119 children, the control group — 320 with newly established T1D. Both groups were comparable in gender and age. T1D manifested with hyperglycemia in 35 (29.4%) patients, with ketosis — in 41 (34.5%), with DKA — in 43 (36.1%) in the study group; and in 81 (25.3%), 89 (27.8%) and 150 (46.9%) patients in the control group, respectively (p = 0.127). DKA was mild in 9 (20.9%), moderate in 24 (55.8%), and severe in 10 (23.3%) patients of study group; and in 36 (24%), 73 (48.7%) and 41 (27.3%) patients in the control group, respectively (p = 0.747).

**Conclusion:** COVID-19 is not associated with the clinical form and severity of DKA at T1D onset.

**Keywords:** children, COVID-19, newly diagnosed type 1 diabetes, manifestation, diabetic ketoacidosis.

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**Fig 1.** Study sample design

Children (aged from 0 to 17) with T1D (n=1585)

Excluded: children with previously known T1D (n=1025)

Children with newly diagnosed T1D (n=560)

Excluded: no data on SARS-CoV-2 IgG level (n=108)

Children with newly diagnosed T1D and known SARS-CoV-2 IgG levels at hospital admission (n=452)

Excluded: laboratory confirmed COVID-19 at hospital admission (n=13)

Enrolled children with newly diagnosed T1D (n=439)

**Note.** T1D (СД1) — type 1 diabetes.

**Table 1**. Comparative characteristics of study groups

|  |  |  |  |
| --- | --- | --- | --- |
| **Indicators** | **Study group (n = 119)** | **Control group (n=320)** | ***p*** |
| Age, years | 10,3 (6,9; 13,1) | 9,2 (5,2; 12,9) | 0,143 |
| Gender (male), abs. (%) | 74 (62,2) | 176 (55,0) | 0,177 |

**Note**. Study group — children with IgG to SARS-CoV-2 ≥10 U/ml at hospital admission with negative test for virus RNA, control group — children with no laboratory signs of COVID-19.

**Table 2**. Clinical manifestation of T1D in children in both groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicators** | **Categories** | **Study group (n=119)** | **Control group (n=320)** | **p** |
| Clinical form of T1D onset, abs. (%) | Hyperglycemia | 35 (29,4) | 81 (25,3) | 0,127(df=2) |
| Ketosis | 41 (34,5) | 89 (27,8) |
| DKA | 43 (36,1) | 150 (46,9) |
| DKA severity, abs. (%)\* | Mild (рН≥7,3) | 9 (20,9) | 36 (24,0) | 0,747(df=2) |
| Moderate (рН=7,1-7,2) | 24 (55,8) | 73 (48,7) |
| Severe (pH <7,1) | 10 (23,3) | 41 (27,3) |

**Note**. T1D (СД1) — type 1 diabetes, DKA (ДКА) — diabetic ketoacidosis. \*Frequency was calculated for the number of patients with DKA in every group. Study group — children who had COVID-19 (IgG to SARS-CoV-2 ≥10U at hospital admission with negative test for virus RNA), control group — children with no laboratory signs of COVID-19.

**Table 3**. Indicators of carbohydrate metabolism during hospitalization, number of treatment days, insulin dosage at discharge, and body weight deficiency in patients with newly diagnosed T1D in both groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicators** | **Reference range** | **Study group (n=119)** | **Control group (n=320)** | **p** |
| HbA1c\*, % | 4,0-6,4 | 11,7 (10,5; 13,2) | 12,0 (10,5; 13,5) | 0,391 |
| Glucose level\*, mmol/L | 3,3-5,5 | 20,7 (14,3; 25,0) | 20,0 (14,8; 27,0) | 0,526 |
| C-peptide\*, pmol/L | 268-1803 | 113,9 (72,1; 170,0) | 103,0 (61,6; 163,2) | 0,117 |
| Number of treatment days | --- | 8,0 (7,0;10,0) | 9,0 (7,0;11,0) | 0,323 |
| Insulin dosage at discharge, U/kg/day | --- | 0,7 (0,5; 0,9) | 0,8 (0,5; 1,0) | 0,124 |
| Body weight deficiency, abs. (%) | --- | 16 (13,4) | 71 (22,2) | 0,041 |

**Note.** \*Blood levels were determined at hospital admission. Study group — children with IgG to SARS-CoV-2 ≥10 U/ml at hospital admission with negative test for virus RNA, control group — children with no laboratory signs of COVID-19.

**RESEARCH LIMITATIONS**

Overall seroprevalence to SARS-COV-2 among children aged 1-17 years in March-August 2020 was about 22% according to Russian data [36]. COVID-19 incidence among children aged 7-14 years in Moscow was about 34% in the same period and 29% in the period from September 2020 to May 2021 [37]. It is comparable to the ratio of children with positive SARS-CoV-2 IgG in our study (28%). However, it should be noted that we have studied sample of hospitalized children living in the Moscow region, and, moreover, 25% of these patients were excluded (108 of them due to no data on SARS-CoV-2 IgG levels and 13 due to laboratory-confirmed COVID-19 on admission). Thus, sample representativeness in this present study remains questionable. Age ratio in our sample (0-14 years — 87.7% (385), 15-17 years — 12.3% (54)) generally corresponds to the all-Russian data on the prevalence: 82.8% (6052) and 17.2% (1260) in 2020, and 83.1% (6790) and 16.9% (1376) in 2021, respectively [38]. Proportion of males with T1D is about 54.1% according to all-Russian data [39], and 56.9% in our study.

The level of <10 U/ml cannot exclude COVID-19 in the past (according to the instructions to reagents set for determining SARS-CoV-2 IgG level). In other words, children in the control group could have undergone the infection. Moreover, test specificity is 93%, so it can show COVID-19 infection presence in some children who have no history of disease. Overall, it could bridge diversities in the compared groups.

It is impossible to balance the compared groups by all interfering factors in observational studies. Therefore, it is possible that groups were comparable by study indicators (clinical forms of T1D manifestation, etc) as the control group was distinguished by the presence or greater severity of factors associated with T1D development. These include viral infections (Coxsackie viruses [23, 24], rubella virus [24], herpes virus, rotavirus [23]), stress [25], short breastfeeding period [26], [27], early nutritional intervention of cow's milk [26, 27, 28] and gluten [29], microbiota composition [29, 30], celiac disease [29].

**Table 4**. Results of international studies on the COVID-19 role in T1D manifestation

|  |  |  |  |
| --- | --- | --- | --- |
| **Study authors** | **Study characteristics** | **Research limitations** | **Conclusions** |
| Denina M. et al. [7] | Objective. Aim of the study — to analyze the correlation of SARS-CoV-2 and T1D and DKA development. Study methods: the presence of current/previous SARS-CoV-2 infection was established via PCR (nasal swab), measuring of SARS-CoV-2 IgG, and questionnaire. Study period: October 2020-April 2021. Design: retrospective cross-sectional study. Sample: 39 people aged 0-14 years. Major results: PCR on SARS-CoV-2 presence was negative in all patients; antibodies to SARS-CoV-2 were revealed in 9 (23%) patients; 16 out of 39 people had NDT1D manifestation with DKA; increased number of DKA cases at NDT1D onset during the pandemic period (risk of DKA was 44% in the pandemic cohort). | - No seroprevalence data in the reference population as no mass screening was performed at the time of the study- No data on children aged 15-18 years | - SARS-CoV-2 infection is potentially associated with the risk of DKA in our population- acceleration of immune process provoked by SARS-CoV-2 may seem more understandable in the development of T1D with DKA |
| Barrett CE et al. [8] | Objective. Aim of the study — to evaluate the risk of T1D, T2D or any other type of diabetes 30 days after SARS-CoV-2 infection in patients <18 years. Study methods: history of infection was established by PCR and ICD-10 code. Study period: March 2020-June 2021 Design: retrospective cohort study. Sample: 891 (95.1%) people aged <18 with NDT1D /NDT2D (IQVIA) and 1,871 (94.8%) people aged <18 years with NDT1D /NDT2D (HealthVerity). Major results: DKA was observed in 33 (48.5%) patients with NDT1D and COVID-19 in the IQVIA database, and in 450 (40.2%) patients in the HealthVerity database. These rates were higher than in NDTD patients without COVID-19. | - Patients infected with SARS-CoV-2 without confirmed diagnosis of COVID-19 or documented positive test result may be verified as having no history of COVID-19 infection- Using one ICD-10 code, thus, there is no way to distinguish different types of diabetes | - DKA was revealed more frequently in patients with COVID-19 than without COVID-19 |
| Rahmati M. et al. [9] | Objective. Aim of the study — to evaluate the risk of NDT1D development in children who had SARS-CoV-2 infection. Study methods: history of infections was established by PCR, some studies included the determination of IgG/IgM to SARS-CoV-2, infection presence was established according to the clinical picture in several studies, and MKB-10 codes were also used. Study period: until March 2023. Design: systematic review and meta-analysis of cohort studies. Sample: 8 reports from 7 studies with 11,220,530 participants (2,140,897 patients with history of SARS-CoV-2 infection and 9,079,633 participants in the respective control groups) were included, all patients aged from 0 to 17 years. Major results: SARS-CoV-2 infection was associated with increased DKA risk in children and adolescents comparing to non-COVID-19 controls. | No data available\* | - SARS-CoV-2 infection is associated with high risk of DKA in children who have undergone COVID-19 |
| Boboc A.A. et al. [11] | Objective. Aim of the study — to analyze differences in NDT1D features in patients with positive and negative SARS-CoV-2 serology. Study methods: history of infection was established via SARS-CoV-2 IgG and/or IgM levels. Study period: April 2021-April 2022 Design: retrospective cohort study. Sample: 158 people with NDT1D <18 years. Major results: ration of patients with DKA in the compared groups (presence/absence of antibodies to SARS-CoV-2) did not differ (p=0.45); also no difference was revealed between the groups in the ratio of children with severe DKA (p=0.81). | - Нет подтверждения, что дети с отрицательными антителами к SARS-CoV-2 не перенесли инфекцию- Небольшой размер выборки исследования; не все изученные переменные были определены у всех пациентов- Высокий риск ошибок типа I, так как несколько одномерных анализов проводились на одном и том же наборе данных | - There were no differences in DKA presence and severity between the patients' groups with positive and negative SARS-CoV-2 serology |
| Salmi H. et al. [12] \* | Objective. Aim of the study — to analyze the risk of hospitalization of patients with DKA correlated to NDT1D during the COVID-19 pandemic. Study methods: history of infection was established by the SARS-CoV-2 IgG and/or IgM levels. Study period: April-October 2016-2020 Design: retrospective cohort study. Sample: 84 children with NDT1D. Major results: the number of hospitalized children in ICU due to NDT1D has increased from 6.25 in 2016-2019 to 20 in 2020 (p<0.001); 33 children had negative test on SARS-CoV-2 antibodies; more children with T1D experienced severe DKA at diagnosis during the pandemic. | - Single center study | - Most children with NDT1D experienced severe DKA during the pandemic that is likely associated to healthcare system limitations during the pandemic  |

**Note.** \*Some statistical data is not described due to limited access to article's full version. T1D (СД1) — type 1 diabetes, NDT1D (ВВСД1) — newly diagnosed type 1 diabetes, T2D (СД2) — type 2 diabetes, NDT2D (ВВСД2) — newly diagnosed type 2 diabetes, DKA (ДКА) — diabetic ketoacidosis, PCR (ПЦР) — polymerase chain reaction, ICD-10 (МКБ-10) — International Classification of Diseases.

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**AUTHORS’ CONTRIBUTION**

**Anastasiya N. Lazareva** — conceptualization, methodology, data curation, formal analysis, investigation, research data visualization, review of scientific publications on the manuscript topic.

**Alexey Yu. Rtishchev** — methodology, investigation, project administration, review of scientific publications on the manuscript topic.

**Irina G. Vorontsova** — methodology, project administration, review of scientific publications on the manuscript topic.

**Irina G. Rybkina** — methodology, project administration.

**Elena E. Petryaykina** — guidance, conceptualization, methodology, data management and analysis, investigation, manuscript review and editing.

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