

Anti-SARS-CoV-2 Seropositivity Among Children With Newly Diagnosed Type 1 Diabetes Mellitus: A Case-Control Study

A sudden increase in the number of children with newly diagnosed type 1 diabetes mellitus (T1DM) was experienced during the third wave of COVID-19 epidemic in Hungary. The newly diagnosed T1DM patients had a significantly higher rate of anti-SARS-CoV-2 positivity as compared to prevalent T1DM children [OR (95% CI) 3.74 (1.08,13.55); $P=0.04$]. The relationship between SARS-CoV-2 infection and diabetes needs to be investigated further.

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Recent reports suggest that increased incidence of type 1 diabetes mellitus (T1DM) may be a consequence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Coronavirus disease 2019 (COVID-19) is primarily characterized by respiratory symptoms, but other organs expressing the angiotensin-converting enzyme 2 (ACE-2) receptor of the viral spike protein may also be affected [3]. Ex vivo and postmortem studies indicate that SARS-CoV-2 can cause pancreatic dysfunction [4]. Centers for Disease Control and Prevention reported a much higher incidence of diabetes (type 1 and type 2) among children with history of COVID-19, than those who did not contract the disease [2]. Our clinical experience showed that the number of newly diagnosed T1DM patients increased remarkably during the spring of 2021. In the previous decades, the incidence of childhood T1DM rose significantly in Hungary; however, in recent years, the annual incidence remained stable, around 22/100,000 children/year [5]. Based on emerging evidence regarding this aspect, we hypothesized that COVID-19 might have been responsible for the rise in new T1DM during this period. So we began systematic testing of new cases of T1DM for the presence of anti-SARS-CoV-2 spike antibody to look for any association.

All children (aged 0-18 years) hospitalized between 1 March, and 15 June, 2021, with new onset T1DM were evaluated for antibody against SARS-CoV-2 spike protein at the time of admission or within three months after discharge. Electrochemiluminescence immunoassay was used for anti-SARS-CoV-2 serology test (Elecsys, Roche) and was considered to be positive above 0.8 μmL . Non-vaccinated, otherwise healthy, known T1DM children of the same Diabetes unit coming for regular checkup during June-July, 2021, were taken as controls. We excluded vaccinated children from both groups to avoid misinterpretation of serology results. The study was performed in accordance with the ethical standards of the Institutional Review Board and with the Declaration of Helsinki.

Statistical analysis was conducted using GraphPad Prism, Version 8.0.1. We compared anti-SARS-CoV-2 positivity between newly diagnosed T1DM patients and prevalent T1DM

children by calculating odds ratios. The level of significance was taken at a P value of 0.05.

A total of 26 new T1DM patients (16 males) with mean (SD) age of 8.53 (5.02) years and 22 controls were enrolled during the study period. In the same period of the last pre-pandemic year (2019), there were 12 new patients, and an average of 17 new patients per year, during the previous five years (2015-2019). All newly diagnosed T1DM children had at least one diabetes autoantibody.

Anti-SARS-CoV-2 test was estimated in 21 new patients, and 11 (52.4%) showed positive results. Among the control group, 22.7% ($n=5$) had serological evidence of previous COVID-19. Thus, the newly diagnosed T1DM patients had a significantly higher rate of anti-SARS-CoV-2 positivity as compared to prevalent T1DM children [OR (95% CI) 3.74 (1.08, 13.55); $P=0.04$]. None of the new T1DM patients with a positive serology had known anamnesis for COVID-19 as per their parents. Of the 26 newly diagnosed T1DM patients, tested for rapid antigen and/or polymerase chain reaction (PCR) at admission, two children had a positive PCR test, one having negative IgG serology for COVID-19, the other did not have a serological test. Various characteristics of the two groups are shown in **Table I**.

Our results indicate that the incidence of childhood autoimmune T1DM increased during the third wave of the COVID-19 epidemic with more than half (52%) of the tested children having a previous coronavirus infection as proven by a positive anti-SARS-CoV-2 serological test. Our findings are in contrast with the results of two studies demonstrating no increase of SARS-CoV-2 seropositivity among newly diagnosed diabetic children [6,7]. However, these studies were conducted during the first year of the pandemic, while we examined our children during the third wave in Hungary.

The proposed theories for association of SARS-CoV-2 and T1DM include the novel coronavirus can induce or accelerate an autoimmune process, the infection could be the last step in an already ongoing progression, which leads to the clinical presentation of T1DM, and SARS-CoV-2 is capable of directly inducing T1DM by the destruction of beta cells. All of our patients had at least one positive autoantibody, indicating no direct beta cell cytopathy. Therefore, based on our results, we hypothesize that SARS-CoV-2 either can accelerate the autoimmune process or it may be the last step which converts latent to manifest T1DM.

A small sample size and a relatively short study period are limitations of our study. The long term epidemiology of T1DM may be affected by different phases of the COVID-19 pandemic.

In summary, our results suggest that during the third wave of COVID-19, a higher proportion of newly diagnosed T1DM children showed serologically confirmed evidence of previous SARS-CoV-2 infections, compared to prevalent cases of T1DM. Further studies and global registries [8] with long follow-ups are

Table I Clinical Characteristics of Children With Newly Diagnosed and Previously Known Type 1 Diabetes Mellitus

Characteristics	Newly diagnosed children (n=21)	Children with pre-existing disease (n=22)	P value
SARS-CoV-2 seropositivity	11 (52.4)	5 (22.7)	0.04
Age (y) ^a	8.84 (4.63)	10.39 (3.46)	0.22
SARS-CoV-2 +ve	9.40 (3.74)	9.92 (1.70)	
SARS-CoV-2 –ve	8.07 (5.51)	10.53 (3.86)	
Male: Female	11 (52.4) : 10 (47.6)	12 (54.55) : 10 (45.45)	0.89
SARS-CoV-2 +ve	3:8 ^c	3:9	
SARS-CoV-2 –ve	8:2 ^c	2:8	
Insulin requirement (unit/kg) ^{a,b}			
SARS-CoV-2 +ve	0.56 (0.20)	–	–
SARS-CoV-2 –ve	0.43 (0.18)	–	–

Data presented as frequency (%) or ^amean (SD). ^b3 months after T1DM diagnosis. ^cP=0.03. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; +ve seropositive, –ve seronegative.

needed to clarify the controversies regarding the correlation of COVID-19 and T1DM.

Ethics clearance: This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the Institutional Review Board (IRB) of the 1st Department of Pediatrics, Semmelweis University who determined that our study did not need ethical approval. Our study has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki.

Contributors: VH: conceptualized and designed the study, analysed and interpreted the results, wrote the manuscript and reviewed and revised the final manuscript; AL,NT,GC: conceptualize and design the study, collected data, interpreted the results, helped draft the initial manuscript; PTH: conceptualized and designed the study, supervised the investigation, analyzed and interpreted the results, wrote the manuscript, reviewed and revised the final manuscript and critically reviewed the manuscript for important intellectual content. He should be approached for raw data. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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