



Pediatric diabetic ketoacidosis as type I diabetes debut with concurrent SARS-CoV-2 infection: A case report

SAGE Open Medical Case Reports
Volume 10: 1–4
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DOI: 10.1177/2050313X221097263
journals.sagepub.com/home/sco



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Abstract

Diabetic ketoacidosis is a life-threatening complication associated with type I diabetes (T1D). Recent evidence suggests that SARS-CoV-2 could trigger diabetic ketoacidosis in type I diabetes susceptibility and previous insulinitis; however, the data on SARS-CoV-2-infected patients with diabetic ketoacidosis as their type I diabetes are still limited. We report a 13-year-old Latinamerican male with symptoms and laboratory tests diagnostic of diabetic ketoacidosis and positive SARS-CoV-2 reverse transcription polymerase chain reaction, who required mild COVID-19 care management, fluid resuscitation, and insulin infusion at a regular dose, without further complications after the acute infection. Clinical/biochemical improvement allowed outpatient endocrinology follow-up with insulin therapy and continuous glucose monitoring. To our knowledge, we report the first case of diabetic ketoacidosis as the debut of type I diabetes in a Colombian pediatric patient with concurrent SARS-CoV-2 infection. Therefore, this report aims to contribute to the global research on SARS-CoV-2 and diabetic ketoacidosis and discuss the approach to these concomitant pathologies.

Keywords

SARS-CoV-2, diabetic ketoacidosis, diabetes mellitus, type I

Date received: 26 January 2022; accepted: 11 April 2022

Introduction

Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by SARS-CoV-2, resulting in a broad clinical spectrum varying from asymptomatic infection and mild symptomatic disease to life-threatening sepsis.¹ The most frequent clinical presentation of the condition is pneumonia; nevertheless, other manifestations include altered glucose metabolism despite preceding metabolic disturbances.^{1,2} SARS-CoV-2 enters human cells through the “spike” surface glycoprotein, binding to angiotensin-converting enzyme 2 (ACE2),³ a receptor that has been proposed as the link between SARS-Cov-2 infection and new-onset diabetes, based on a possible direct infection to the pancreatic islets evidenced with in-vitro humans models showing permissiveness of pre-b-cells to the virus.⁴ In essence, this virus could generate pancreatic cell injury that presumably decreased insulin production.⁵

Regarding the heterogeneous glucose metabolism disturbances related to SARS-CoV-2, mild-to-severe hyperglycemia is reported with or without ketoacidosis and is suspected

to be associated with physiopathological factors and steroid use during the infection.² There is a relationship between any

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form of hyperglycemia and a poor prognosis following SARS-CoV-2 infection.² Besides, diabetic ketoacidosis (DKA) is a life-threatening metabolic disorder defined by a relative or absolute insulin deficiency associated with stress or sickness.⁶ The biochemical criteria based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) include the presence of blood glucose > 200 mg/dL, a venous pH < 7.3 , or serum bicarbonate < 15 mmol/L, and ketonemia or ketonuria.⁷ The evidence of SARS-CoV-2-infected patients presenting with DKA as their debut of type 1 diabetes (T1D), is still limited. This report presents the clinical scenario of a pediatric patient in the Colombian population, aiming to discuss fundamental aspects of the approach to patients presenting with these diseases concomitantly.

Case description

We present a 13-year, 11-month-old male without relevant past personal or familial medical history, who attended the emergency room with 1-month polydipsia, polyuria, dysphagia, emesis, and 7-kg weight loss, associated with retrosternal chest pain and dyspnea exacerbated in the last week previous to admission. Initial physical examination revealed grade II dehydration, mottled skin, no fever, tachycardia, mild hypertension, and polypnea; a glucose test in the emergency room revealed hyperglycemia (353 mg/dL), without clinical signs of cerebral edema. Admission laboratory test reports (Table 1) included elevated glycated hemoglobin (A1c), severe metabolic acidosis, and complete blood count showed hemoconcentration secondary to dehydration, without white blood cells or platelet count abnormalities.

The patient was admitted to the Pediatric Intensive Care Unit (PICU) on the first day of admission, where a SARS-CoV-2 reverse transcription polymerase chain reaction (rt-PCR) test was performed as part of PICU protocols with a positive report, presuming 5–7 days of the viral disease, requiring risk assessment laboratories (Table 1). An increased D-dimer blood concentration, negative troponin test, normal serum procalcitonin, ferritin, and lactic dehydrogenase, with electrolytes, and chest X-rays without pulmonary abnormalities were evidenced. Other laboratory tests included normal serum electrolytes and liver enzymes; no pancreatic enzymes were measured. He required initial fluid resuscitation, insulin infusion (0.05 UI/kg/h), and low-flow supplemental oxygen therapy (0.5 L/min). During in-patient treatment, no additional complications related to SARS-CoV-2 infection emerged, allowing discontinuation of supplemental oxygen therapy. Due to clinical and acidosis recovery, the patient was allowed to continue subcutaneous intensive insulin therapy and received education regarding the ambulatory treatment of T1D. He was discharged on the ninth day following the admission and continued outpatient follow-up by the pediatric endocrinology department with a continuous flash

glucose monitoring device without further complications (Figure 1).

Discussion

T1D is a complex metabolic entity involving genetic and immunological components, which environmental triggers can contribute to disease development.⁸ Frequently, T1D is characterized by pancreatic islet inflammation (insulinitis), progressing to total β -cells apoptosis. Hence, T1D emerges from chronic β -cell autoimmune attack, where the local release of inflammatory mediators and infiltration of immune cells may represent a critical role.⁹ When approximately 90% of β -cells are impaired, insulin deficiency reflects clinically, progressing until patients are insulin-dependent.⁹ The presence of a marked insulin deficiency could be evident during devastating immune responses, causing a rare fulminant presentation of new-onset T1D with hyperglycemia and DKA.⁹

Several viruses are proposed to trigger an initial autoimmune attack, promoting an intense inflammatory response and pancreatic lesions accompanied by pancreatic viral replication. The hypothesis of particular viruses triggering an autoimmune reaction against pancreatic β -cells is predominantly associated with enterovirus species and rubella, mumps, parainfluenza, and human herpesvirus type 6.⁹ Evidence suggests that the pathogenesis of SARS-CoV-2 could promote the development of DKA, and thus non-diagnosed T1D identification.^{1–12} Although this relationship is not entirely understood, it is not possible to distinguish if it is a consequence of viral activity or the immune response related to T1D. In addition, T1D implies a massive inflammatory component, with increased deregulated pro-inflammatory cytokines (IL-1, IL-6, and tumor necrosis factor) also involved in the pathophysiology of COVID-19.^{3,11} Increased D-dimer and C-reactive protein have also been denoted in T1D and COVID 19, which is coherent with the laboratory findings in our patient.^{3,9}

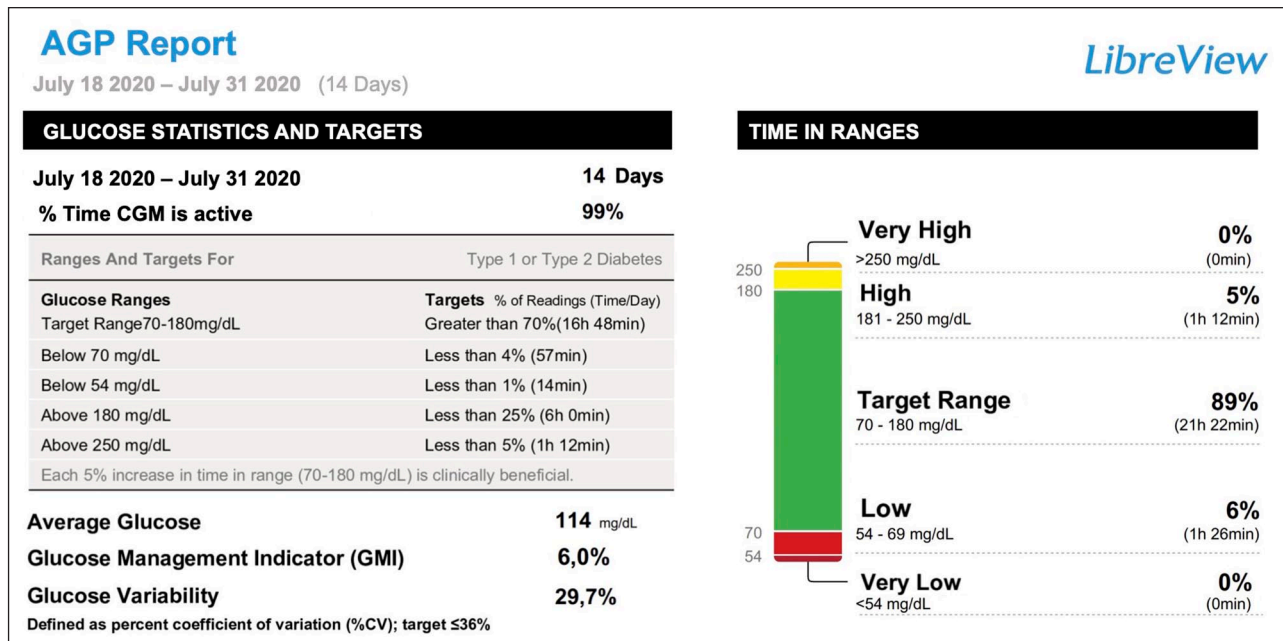
Given the current health situation regarding the SARS-CoV-2 pandemic, several research data have shown increased pediatric DKA rates during the pandemic compared to the pre-pandemic era. This was documented in a pediatric German population with a new-onset T1D diagnosis, observing a monthly DKA rate of 22.6% in January 2020, increasing to 43.3% in August 2020.¹² DKA frequency from middle march until late June 2020, comparing the same periods within 2017, 2018, and 2019 in Israeli pediatric diabetes centers, showed a dramatic surge in new-onset T1D presenting DKA, with an increased incidence of 58.2% during 2020.¹³ Therefore, suggesting the proposal of the virus as a potential trigger for DKA development.¹

Regarding SARS-CoV-2 infection, hyperglycemia has a multifactorial etiology and different metabolic effects among patients with and without past metabolic history. β -pancreatic

Table 1. Laboratory test results.

Laboratories	Results	Date
Plasma glucose	363 mg/dL	Day of admission
Glycated hemoglobin (A1c)	12.6%	
Venous blood gases	pH 7.09, HCO ₃ 7.2 mmol/L, Anion Gap 32, Lactate 3.04 mmol/L	
Complete blood count	Leucocytes 10,800, Neutrophils 8000 (74.3%), Lymphocytes 1960 (18.2%), Monocytes 690 (6.36%), Hemoglobin 18.2g/dL, Hematocrit 52.6%, Platelet count 265.000	
Reactive C-protein	0.1 mg/dL	
D-dimer	1.2 mg/L	
Serum procalcitonin	0.05 ng/mL	
Troponin I	0 ng/mL	
Serum ferritin	182.36 ng/mL	
Lactic dehydrogenase	163 U/l	
Serum fibrinogen	293 mg/dL	
SARS-CoV-2 rt-PCR	Positive	
Liver enzymes	Alanine transaminase 16 U/l, Aspartate transaminase 18 U/l	

rt-PCR: reverse transcription polymerase chain reaction.

**Figure 1.** Continuous glucose monitoring during initial outpatient follow-up.

cell damage is recognized indirectly in the post-infectious phase with DKA development days after acute infection.¹⁰ The association between COVID-19 and the increase of T1D diagnosis has been proposed in the United States, United Kingdom, Germany, Italy, and India, among other countries.¹⁻¹² In Latin America, two other case reports of pediatric COVID-19 were associated with DKA; however, the first patient had obesity and familiar history of type 2 diabetes¹⁴ and the second had a 3-year history of diagnosed T1D with prior insulin administration.¹⁴ On the contrary, our patient had no previously known metabolic disturbances or

a familiar history of metabolic or autoimmune disease. Despite his 1-month clinical history and the evidence of increased HbA1c, his symptoms worsened 1 week before, which can correlate with suspected DKA precipitation by SARS-CoV-2.¹⁴

Conclusion

Up to date, evidence portrays SARS-CoV-2 as a possible trigger for DKA and T1D debut. This can be reflected on reports showing a surge on DKA rates, compared to pre-pandemic

era, in patients with or without a metabolic diagnosis. This patient showed increased A1C, implying at least 2–3 months of not previously known metabolic disturbances. Although he had a mild COVID-19 presentation without severely increased disease markers, the onset of the infection could be associated with the precipitation of his symptoms before in-patient treatment. Future research should be focused on determining the overall relationship of the SARS-CoV-2 virus in the new-onset T1D and establishing the incidence of DKA in the presentation of SARS-CoV-2 infection.

Acknowledgements

The authors thank Karen Moreno-Medina, coordinator of scientific production and general supervisor of the research, and Fredy Luna-Vela, MD, scientific advisor.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case was obtained from Fundación Cardioinfantil—La Cardio ethics committee and institutional review board. ID: ACTA #17-2021.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the legally authorized representative of the patient.

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