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Case Report

The Perfect Storm: Rapid Progression of Diabetic Ketoacidosis in Pediatric Diabetes in the Setting of COVID-19



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ABSTRACT

Objective: The coronavirus disease 2019 (COVID-19) pandemic has introduced countless challenges to the medical field. Although pediatric patients have been reported to have lower rates of COVID-19 mortality, the presence of pre-existing conditions can heighten the severity of their clinical presentation. This report discusses the potential influence COVID-19 might have on diabetic ketoacidosis.

Methods: Our patient, a 6-year-old girl with known type 1 diabetes, presented with acute onset of abnormal breathing and altered mental status. The day prior, she had 1 episode of emesis, diarrhea, and abdominal pain but no fever. She presented to an outside hospital and was reported to have agonal breathing with a Glasgow Coma Scale score of 8 (eyes open to pain, no verbal response to stimuli, and localized pain). She was promptly intubated, and the initial laboratory tests revealed severe diabetic ketoacidosis (DKA). A family member had COVID-19, and she also tested positive for COVID-19.

Results: Our patient's rapid progression and severity of illness require a discussion of how COVID-19 might affect diabetes and indicate opportunities for improving clinical practice in children with pre-existing diabetes. We discussed how COVID-19 might change the underlying pathophysiology of DKA and cause metabolic complications. Possible mechanisms include binding to angiotensin-converting enzyme 2 receptors and enabling a proinflammatory "cytokine storm." Additionally, ketoacidosis and altered mental status have been present in patients with COVID-19 without diabetes, which might potentiate the symptoms in developing DKA.

Conclusion: Prompt recognition of DKA is warranted, as caregivers may attribute the symptoms to COVID-19 rather than to DKA, resulting in an increased severity of illness on presentation with acute symptom onset, as described in this report.

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Introduction

Since December 2019, our world has been racing against time in the search for answers about, treatments of, and prevention of coronavirus disease 2019 (COVID-19) as millions of people have been affected. Pediatric COVID-19 cases can present in a variety of

ways, with the most common symptoms being fever, cough, respiratory distress, gastrointestinal symptoms, and headaches. Although children with COVID-19 have lower morbidity and mortality rates than adults with COVID-19, our focus is drawn to patients with a pre-existing diagnosis, such as diabetes, and how COVID-19 might worsen their disease course. Several factors can explain why pediatric patients with diabetes might have worse clinical presentations of DKA when also diagnosed with COVID-19.

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; IL-6, interleukin 6; SARS-CoV, severe acute respiratory syndrome coronavirus.

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Case Report

Our patient was a 6-year-old girl with type 1 diabetes diagnosed 6 months prior to this admission. The initial diagnostic laboratory test results were positive for glutamic acid decarboxylase with a level of

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0.25 nmol/L (normal value, <0.02 nmol/L) and negative for insulin antibodies (normal value, <0.02 mmol/L), islet antigen-2 antibodies (normal value, <0.02 mmol/L), and zinc transporter 8 autoantibodies (normal value, <15.0 U/mL). Moreover, test results revealed a C-peptide of 0.3 ng/mL, a blood glucose of 555 mg/dL, an HbA1c of 10.9% (96 mmol/mol), a β -hydroxybutyrate of 3.21 mmol/L (normal value, <0.40 mmol/L), a pH of 7.35, a bicarbonate of 21 mEq/L, and an insulin requirement of <0.5 IU/kg/d (in honeymoon phase). On this admission, she presented to an outside hospital from home owing to an acute onset of abnormal breathing and altered mental status. The day prior, she had 1 episode of emesis, diarrhea, and abdominal pain but no fever, and her glucose levels were over 400 mg/dL. A known COVID-19-positive contact in the household was reported. The initial vital signs were a temperature of 36.5 °C, pulse rate of 152 beats/min, respiration of 46 cycles/min, blood pressure of 133/88 mm Hg, oxygen saturation of 100%, weight of 21.3 kg (34%), height of 117 cm (47%), and body mass index of 15 (37th percentile). On arrival, her Glasgow Coma Scale score was 8 (eyes open to pain, no verbal response to stimuli, and localized pain), and she was reported to have agonal breathing. Almost immediately, the patient was intubated. Remarkable laboratory test results included a glucose level of 486 mg/dL, venous blood gas with a pH of 6.88, bicarbonate of 4 mEq/L, lactate of 5.8 mmol/L (normal value, 0–1.0 mmol/L), β -hydroxybutyrate of 11.9 mmol/L, and anion gap of 29 mEq/L, which were significantly worse than the results she had during the initial diagnosis of type 1 diabetes 6 months earlier. She was diagnosed with severe diabetic ketoacidosis (DKA), and treatments with isotonic fluids and insulin were initiated. Owing to concern for cerebral edema, given the acute change in her mental status, she was administered a dose of mannitol. At this point, her polymerase chain reaction test result for severe acute respiratory syndrome coronavirus (SARS-CoV) 2 returned positive. She was then stable enough to be transferred via a flight to a higher level of care at our center. Due to a concern for possible multisystem inflammatory syndrome in children, laboratory tests were performed, including ferritin, D-dimer, brain natriuretic peptide, lactate dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, troponin, hepatic function panel, and coagulation studies. The results of these laboratory tests were largely normal with the exception of an elevated D-dimer of 1112 ng/mL (<500 ng/mL). She was suitable for extubation approximately 12 hours later with the return to her baseline mental status and with improved acidosis. She was transitioned to subcutaneous insulin on day 2 of her hospital stay. On day 3 of hospitalization, she had a sore throat, productive cough, fatigue, headache, and fever (maximum of 39.5 °C) that persisted for 4 more days until she was afebrile, had improved oral intake, and was subsequently discharged home in good condition.

Discussion

The rapid progression of symptoms in this patient prompts the question of whether COVID-19 may, in fact, be associated with a more severe presentation than other more common infectious agents in pediatric patients. To further understand the connection, the pathophysiology of COVID-19 and its relation to DKA needs to be explained.

Renin-Angiotensin-Aldosterone System

One suspected interaction of COVID-19 is with the renin-angiotensin-aldosterone system. The angiotensin-converting enzyme 2 (ACE2) is expressed in large quantities in the lung, intestine, and pancreas, to name a few. Its role is to convert

angiotensin II to angiotensin, which contributes to a decrease in inflammation, an increase in insulin, and vasodilation.¹ SARS-CoV-1, the virus responsible for the severe acute respiratory syndrome outbreak in 2003, has been proven to bind to ACE2 via the spike protein.² It would be reasonable to propose that as a relative of SARS-CoV-1, COVID-19 might cause the downregulation of ACE2 upon binding and destruction of the islet cells.^{3,4} This downregulation could then lead to an increased level of angiotensin II, which plays a known role in insulin resistance.⁵ Additionally, angiotensin II is a factor in endothelial dysfunction, leading to oxidative stress and further triggering inflammatory factors.⁵

Our patient was receiving only 0.5 U/kg/d of insulin because her diabetes was diagnosed just 6 months earlier, meaning, she likely had some degree of functioning islet cells prior to her illness, also referred to as the “honeymoon period.” At the postdischarge follow-up, she was receiving closer to 1 U/kg/d of insulin. She was not reported to have elevated glucose levels at her visits prior to this presentation, signifying that her increased insulin needs were less likely due to noncompliance. The potential destruction of islet cells due to COVID-19 could have both acutely worsened her DKA as well as hastened the natural progression of her remaining pancreatic cell function.

Cytokine Storm

Another connection between these 2 disease processes is the inflammatory markers that are present. The cytokine interleukin 6 (IL-6) has been shown to be elevated in patients with COVID-19 due to the hyperinflammatory state, independent of DKA. IL-6 has also been reported to be elevated in patients with DKA as a driver of ketogenesis.⁶ With both disease states occurring simultaneously, it is possible that the patient’s overall inflammatory response may create a worse clinical status compared with other precipitating agents. Unfortunately, the IL-6 level was not collected for the patient described here.

Ketosis

Pathologic ketosis and ketoacidosis can be seen in various disease states such as DKA, starvation, and toxin ingestion, among others. In diabetes alone, decreased insulin levels will induce the ketogenesis pathway. When patients become ill, there is a higher level of counterregulatory hormones such as epinephrine, which has been shown to induce lipolysis, activating ketogenesis.⁷ A study that was completed in early 2020 retrospectively collected data from 658 hospitalized patients with COVID-19 and recorded the incidence of ketosis and ketoacidosis in the cohort.⁸ Results revealed that 6.4% of patients had ketosis on admission, with only 35% of those patients having diabetes. COVID-19 is believed to potentiate fat breakdown, leading to ketosis and ketoacidosis.⁸ This suggests that COVID-19, independent of DKA, could cause ketosis and, potentially, ketoacidosis in severe disease.

Ketoacidosis can have detrimental effects on cellular functioning as oxidative stress is known to be induced by ketones in many different cell types. Additionally, ketones can contribute to insulin resistance by downregulating the cell surface insulin receptor and the phosphorylation of the insulin receptor substrate-1.⁷ The exact mechanisms of COVID-19 and ketosis are not specifically defined yet; however, the 2 proposed mechanisms of illness and decreased insulin reserve could have been secondary to the synergistic effect, worsening her clinical status.

Altered Mental Status

Finally, it is important to recognize that the initial symptoms reported by our patient were not respiratory but rather gastrointestinal and neurologic symptoms manifested as emesis/diarrhea and altered mental status, respectively. In patients with DKA, altered mental status has been shown to be related primarily independently of acidosis.⁹ A surveillance study completed in the United Kingdom identified altered mental status as a symptom in 31% of patients with COVID-19, which was disproportionately more common in younger patients (labeled as those under 60 years of age).¹⁰ Studies have shown that SARS-CoV, a relative of COVID-19, is able to access the brain with positive results of polymerase chain reaction testing and with positive findings in the cerebrospinal fluid of affected patients.¹¹ The proposed mechanism is the access via the ACE2 cells, as mentioned above. Additionally, the binding affinity of COVID-19 was reported to be 10 to 20 times higher than that of SARS-CoV.¹¹ Numerous neurologic complications due to COVID-19 are being reported with only potential mechanisms being speculated. Although our patient's rapid change in mental status could be explained by acidosis, as noted in our patient's laboratory test results, a contributing factor of COVID-19 could also exist.

Conclusion

While data involving pediatric cases of COVID-19 precipitating DKA are produced, it is important to understand the potential presentation of the overlap of COVID-19 and DKA. The Type 1 Diabetes Exchange Quality Improvement Collaborative studied patients from 49 clinics in the United States and found that 45% of patients with confirmed COVID-19 had DKA, which highlights the importance of recognizing symptoms.¹² Emphasis needs to be placed on strict "sick day rules" at the first sign of illness. A confusing picture is painted when parents may recognize symptoms of COVID-19 rather than DKA, resulting in late recognition when acute symptoms occur, as described in this case. More data will need to be collected to fully understand the pathophysiology of COVID-19 and how exactly it might worsen DKA. To date, research suggests that it may cause an increase in inflammatory markers, a decrease in insulin secretion secondary to the downregulation of ACE2 and destruction of islet cells, an increase in insulin resistance, and an increase in ketosis and ketoacidosis and potentially lead to altered mental status.^{3,6,8,11} Further research into these proposed

mechanisms could better guide the management of patients as well as introduce targeted treatments.

Author Contributions

P.G.B., G.H., M.D., and C.O. provided writing assistance for and proofread this report.

Disclosure

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