COVID-19 in two children with new-onset diabetes: case reports

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SUMMARY

Delayed diagnosis, low socioeconomic status and infection have been associated with diabetic ketoacidosis (DKA) at type 1 diabetes mellitus presentation. A teenager from a low socioeconomic status family, with longstanding weight loss, polyphagia, polyuria, vomiting and abdominal pain, attended the emergency department, also complaining of anosmia and odynophagia. He was diagnosed with COVID-19 and new-onset DKA. The second child had 2 weeks of diabetes symptoms and was admitted with new-onset mild DKA. SARS-CoV-2 RT-PCR test was positive, although asymptomatic. Persistent hyperglycaemia with high insulin requirements was a common feature to both patients. Both cases support that SARS-CoV-2 may have an association with rapidly increasing insulin daily needs. In case one, not only fear of COVID-19 delayed hospital attendance but also the setting of a low socioeconomic status family appears to have enhanced the risk for late diagnosis and challenging disease management.

BACKGROUND

Type 1 diabetes mellitus (T1DM) is one of the most prevalent endocrine diseases in childhood.[1] Diabetic ketoacidosis (DKA) is an acute life-threatening complication of both new-onset and previously settled T1DM.[2] Disease presentation with DKA has been associated with delayed diagnosis, absence of family history of diabetes, low socioeconomic status, younger age and preceding infection.[3–6]

During COVID-19 outbreak, there was a significant reduction in paediatric emergency department (PED) visits, in the setting of fear of SARS-CoV-2 infection.[7–9] In fact, there are concerns that parents delayed seeking emergency help for children with symptoms of diabetes, which may have resulted in increased severe T1DM presentations, namely DKA.[7 10]

In the UK, a national survey found that the proportion of new-onset T1DM presenting with DKA was higher than previously reported.[11] A significant increase (85%) in DKA and severe DKA at T1DM diagnosis in children and adolescents during the COVID-19 pandemic was also described in Germany.[12] On a web-based survey on the early phase of the COVID-19 pandemic in Italy, there were also more cases of new-onset severe DKA when compared with 2019.[7] These data point towards a role of delayed diagnosis on the severity of presentation.

Seasonal viruses have been proposed as a precipitating factor for T1DM since more than 40 years ago.[13] Indeed, seasonal variation in T1DM presentation can partially be explained by the seasonal variation of viral infections.[14] More than 14 different viruses have been reported to be implicated in the pathogenesis of T1DM.[15] *Rotavirus* has shown a tropism towards pancreatic beta cells, promoting its infection and disease induction.[16] Coxsackievirus usually affect children in late summer and early autumn and *Rotavirus* has a peak in the winter months, which corresponds to the most frequent time frame for seroconversion or the first appearance of T1DM autoantibodies.[14]

It was postulated that SARS-CoV-2 exposure could also have contributed to an increased incidence in cases by precipitating or accelerating T1DM[17] and possibly contributing to the diagnosis of previously unrecognised diabetes.[18] A combination of different factors related to COVID-19 may increase the risk of developing or the progression of type 1 or 2 diabetes.[19]

SARS-CoV-2 binds to angiotensin-converting enzyme 2 receptor (ACE2r), expressed in specific tissues in the human body, including lungs, small intestine, adipose tissue, kidneys and pancreas.[18 20–22] It is more infective and has more affinity for ACE2r that the previously known SARS-CoV, and it uses this specific receptor for pancreatic beta-cell entry,[20] possibly leading to direct cell injury and insulin deficiency.[18]

Also, an immunological dysregulation by SARS-CoV-2 potentially leading to an autoimmune attack to islet cells mimicking pancreatic cell destruction in T1DM was suggested.[23]

Hyperglycaemia is a known complication of SARS-COV-2 infection, and it has been reported both in diabetic and non-diabetic patients infected with SARS-CoV-2.[24] In fact, glycaemic deterioration is a complication of COVID-19 in patients with diabetes, possibly even inducing DKA.[25 26] In patients requiring insulin, SARS-CoV-2 infection has been associated with higher insulin levels at the peak of COVID-19 illness.[18] It has been hypothesised that there is a potential diabetogenic effect of COVID-19, which seems to go beyond the severe illness stress response.[21]

CASE PRESENTATION

Case 1 presentation

Case 1 is a 13-year-old boy from an immigrant family, living temporarily at a friend's house with his mother and brother. His mother had T1DM since the age of 35 years, with poor metabolic control. Both his mother and brother reported anosmia and dysgeusia since the previous week.

He was brought to the PED reporting a 2-month history of progressive non-intentional weight loss (16% of previous weight), polyphagia and polyuria. In the past week, he had developed abdominal pain, sporadic non-bilious vomits, diarrhoea and progressive weakness. When unmeasured fever, nasal congestion, anosmia and odynophagia began a few days later, he was eventually taken for evaluation at the PED.

At hospital admission he appeared ill, malnourished and clinically dehydrated. He was afebrile, tachycardic and tachypneic and both blood pressure and peripheral oxygen saturation were normal. Cardiopulmonary auscultation and abdomen exploration were normal. On laboratory evaluation, he had severe hyperglycaemia (517 mg/dL), with elevated ketonaemia (5,8 mmol/L) and metabolic acidosis (pH 7.18, serum bicarbonate 11.6 mmol/L), and concomitant acute renal injury (creatine 1.38 mg/dL). Further initial evaluation revealed haemoglobin A1C (HbA1C) 15.3%, low C peptide (0.4 ng/mL, normal reference values 0.9–7.1 ng/mL), positive anti-glutamic acid decarboxylase (GAD) antibodies (6.9 U/mL) and hypercholesterolemia (total cholesterol 233 mg/dL). Blood count, C-Reactive Protein (CRP), procalcitonine (PCT) and chest X-ray were normal.

He was hospitalised with the diagnosis of new-onset diabetes with moderate DKA. Intravenous hydration with saline was started, followed by insulin perfusion, according to the DKA protocol, with adequate progressive correction of the acidosis. There were no acute metabolic or neurologic complications. Subcutaneous intensive insulin treatment was started with a basal-bolus regimen with glargine and lispro. There was a marked tendency for hyperglycaemia with progressively rising needs of total daily insulin dose, which peaked at 1.7 U/kg/day on the 8th day of hospitalisation, decreasing thereafter to 0.9 U/kg/day. By then, he was clinically well and could be discharged home if he could continue in isolation. Nevertheless, public health department home visit determined that there were no conditions to isolation, so he had to remain hospitalised. Diabetes management was made difficult because of the mother's misbeliefs, inaccurate diabetes care procedures and the absence of physical activity determined by the bedroom confinement. Episodes of anxiety, crying and sadness related to difficulty in managing the newly diagnosis of diabetes and fear of COVID-19 complications prompted pedopsychiatry evaluation and psychological support.

COVID-19 diagnosis was assumed because of clinical aspects and family context (mother and brother both tested positive to RT-PCR SARS-CoV-2 test); however, he tested inconclusive and negative on the first two nasal and oropharyngeal swab tests, testing positive only on the third evaluation. During hospitalisation presenting symptoms resolved, and insulin was the only pharmacologic intervention.

After 17 days of hospitalisation, after negative PCR for SARS-CoV-2, he was discharged, on a multiple daily injections insulin regimen, supported by a bolus-calculator glucose meter.

Case 2 presentation

Case 2 is a previously healthy 8-year-old boy, presenting to the PED with complaints of polyphagia, polyuria with nycturia and a non-quantified weight loss since the last 2 weeks. At the beginning of symptoms, he had unmeasured sensation of fever for 48 hours.

At hospital admission he appeared moderately ill, was afebrile and was mildly dehydrated. On laboratory evaluation, he had severe hyperglycaemia (552 mg/dL), with elevated ketonaemia (7 mmol/L) and mild metabolic acidosis (pH 7.21, serum bicarbonate 13.1 mmol/L). There was also acute renal injury (creatine 0.82 mg/dL) in the setting of dehydration. Further initial evaluation revealed: HbA1C 12.4%; undetectable C peptide (<0.1 ng/mL, reference value: 0.9–7.1 ng/mL) and positive anti-GAD antibodies (1.3 U/mL, negative<1,0 U/mL). Blood count and CRP were within normal range. Intravenous hydration and insulin treatment according to DKA protocol were started, with progressive correction of acidosis.

Routine RT-PCR SARS-CoV-2 test at admission was positive, although his cohabitants were asymptomatic, and his mother tested negative at hospital admission. He was transferred to our hospital to a COVID-19-dedicated ward with the diagnosis of new-onset DKA and COVID-19. During hospitalisation, a marked tendency to hyperglycaemia was noticed, with increasing needs of daily insulin dose, which peaked 1.6 U/kg/day on the 4th day of hospitalisation. After discharge from the hospital, there was a fast decrease in insulin requirements, leading to frequent hypoglycemic events before adjustments to the prescribed insulin doses.

DISCUSSION

We report two cases of new-onset T1DM in an adolescent and a child, both with concomitant COVID-19 at disease presentation.

In the first case, fear of COVID-19 infection in the pandemic setting accounted for the delay in seeking for medical help. The fact that the adolescent mother was an insulin-treated diabetic could have prompted an earlier recognition of diabetes symptoms and rapid attendance to the emergency department. Indeed, family history of diabetes has been reported as a protective factor of DKA at T1DM presentation, as shown in a 2011 systematic review on the factors associated with DKA in new-onset T1DM in children.[1 3]

On the contrary, in case one, early diabetes symptoms went unrecognised or undervalued, and the family only attended the PED because of emerging COVID-19 symptoms. Moreover, his mother's misbeliefs regarding diabetes basic care became a barrier to inpatient diabetes management and therapeutical education by the healthcare team. This case also highlights the importance of parental care during adolescence and how strongly a structured family environment contributes to achieving good metabolic control.[27]

Both patients had diabetes presenting as DKA with concomitant COVID-19 and both developed progressively higher daily insulin needs although they only manifested mild COVID-19 symptoms.

Two cases of 4-year-old and 7-year-old children, both previously healthy with concomitant new-onset diabetes and COVID-19, have been published. The authors reported only light symptoms of COVID-19 and negative C-Reactive Protein (CRP) and PCT. Information regarding insulin daily needs was not provided by the authors. One of the patients had hypoglycaemia after discharge, which led to insulin dose reduction, similar to what happened in our cases.

The authors highlight that COVID-19 may have a potential diabetogenic effect in addition to the common illness stress response.[28] Our report also supports this finding. The hypothesis that the pleiotropic effects of SARS-CoV-2 on glucose metabolism may exceed the stress response related to symptoms and disease severity has also been stated by other authors.[21] The mechanisms contributing to high insulin daily needs in both our patients during the acute COVID-19 illness may go beyond the disease-related stress response itself. In fact, neither of our patients had moderate or severe COVID-19 symptoms

and both had negative markers of inflammation on their laboratory results. A possible explanation may rely on the interaction between SARS-CoV-2 and the renin–angiotensin–aldosterone system.[28] Studies on the pathogenesis of glucose intolerance in patients with SARS-CoV-2 infection have uncovered that SARS-CoV-2 uses ACE2r as cellular entry point. The higher the level of expression ACE2 in the organs, the greater the level of damage by SARS-CoV-2. Researchers found that SARS-CoV-2 damages correlated with ACE2 expression in different organs, as pancreas, possibly by damaging islets cells.[29] Another possible mechanism to explain this hypothesis is an exaggerated proinflammatory cytokine response secondary to SARS-CoV-2 infection. Both by triggering proinflammatory cytokines as interleukin-6 or by enhancing autoimmune pancreatic cell destruction in genetically predisposed individuals.[19 23]

Nevertheless, more investigation is needed in order to evaluate the possible associations between new-onset T1DM and COVID-19. An international group on diabetes research established a global database called CoviDiab Registry Project to collect data of patients with COVID-19-related diabetes with the aim to investigate the interaction between these two conditions and elucidate possible underlying mechanisms.[21]

Learning points

- Delaying the pursue of medical attention in the pandemic era may have resulted in more severe disease presentations.
- Low economic status may convey a risk for late diagnosis and complicated chronic disease management.
- SARS-CoV-2 may have a role in accelerating type 1 diabetes mellitus (T1DM) and is associated with increased insulin daily doses that may exceed the stress response related to the disease.
- Fear of COVID-19 may contribute to delay in seeking medical support, interfere with new-onset T1DM presentation and complicate hospitalisation with anxiety and emotional distress.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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