

Newly-onset type 1 diabetes mellitus precipitated by COVID-19 in an 8-month-old infant

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Summary. Type 1 diabetes mellitus (T1DM) is rare in infants and toddlers and is usually associated with a relatively high mortality when complicated with diabetic ketoacidosis (DKA). In infants, the classical symptoms of DKA are atypical and therefore many infants with DKA are mistreated for infections. We report a case of DKA precipitated by COVID-19 in an 8-month-old infant with newly diagnosed diabetes mellitus. This case is reported in view of its rarity and originality. The relation between T1DM and COVID19 infection is discussed. (www.actabiomedica.it)

Key words: diabetic ketoacidosis, SARS-CoV-2, COVID-19, atypical symptoms, ACE 2

Background

COVID-19 is a viral disease that can affect every age group - from infants to the elderly - resulting in a wide spectrum of various clinical manifestations. COVID-19 might present different degrees of severity - from mild or even asymptomatic carriers, even to fatal cases. The most common complications include pneumonia and acute respiratory distress syndrome (1). In some cases, infected infants or children might present atypical symptoms, such as gastrointestinal manifestations (2). To date, the majority of primary transmission of COVID-19 for children has been observed to occur within family clusters (3). SARS-CoV-2 (which causes COVID-19 enters human cells via the envelope spike glycoprotein, which is also responsible for host-to-host transmission (4). This glycoprotein, which is found on the surface of the virus, binds to the ecto-enzyme angiotensin-converting enzyme 2 (ACE2; located on human cells) to gain entry into the cell (5). As the human endocrine pancreas expresses ACE2, the coronavirus might enter islets and cause acute β -cell dysfunction, leading to acute hyperglycaemia (4).

A case of overt diabetic ketoacidosis (DKA) precipitated by COVID-19 is reported in view of its rarity. The relation between diabetes mellitus type 1 and COVID-19 infection is discussed.

Case report

An 8-month-old Jordanian infant was admitted to the Emergency Department (ED) of Hamad General Hospital, Doha (Qatar) because of two days history of fever, vomiting, 10% dehydration and rapid breathing. At admission, he was haemodynamically stable but had tachycardia and tachypnea. He did not display Kussmaul's breathing and did not require supplemental oxygen. On examination at ED, his temperature was 38.5°C, weight: 9.3 kg, length: 71.5 cm and weight for length: 1.4 SDS. Laboratory investigations were significant for hyperglycaemia, and overt DKA. Upon further investigation, the parents admitted contact with a defined case of COVID-19. A chest radiograph resulted negative and a nasopharyngeal swabs for an RT-PCR to test for SARS-CoV-2 resulted positive as well as for both parents (Table 1).

Table 1. Laboratory results

Investigation	Result	Reference Range
Venous glucose (mmol/L)	31.7 (571 mg/dL)	–
Venous blood gas		
pH (mmHg)	7.08	7.25–7.35
Bicarbonate (mmol/L)	2	22–28
pCO ₂ (mmHg)	14	35–45
Sodium (mmol/L)	130	135–145
Chloride (mmol/L)	105	95–110
Base Excess	-20.5	-2-2
β-Hydroxybutyric acid (mmol/L)	6.4	<0.3
Creatinine (μmol/L)	42	15-37
Glycated haemoglobin (%)	8.5%	Up to 5 %
D-Dimer (mg FEU/L)	0.63	0 – 0.44
Fibrinogen (g/L)	1.49	1.6 -4
APTT (seconds)	27.2	24-33
Ferritin (μg/L)	28.9	12.0-57.0
C- Reactive Protein (mg/L)	4.2	0.0-5.0
Procalcitonin (ng/mL)	0.23	< 0.15

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Table 1. Laboratory results

Investigation	Result	Reference Range
C-Peptide (ng/mL)	0.43	0.50-5.50
TSH (mIU/L)	1.07	0.70-8.40
FT4 (pmol/L)	11.7	11.6-25.7
Insulin (μ UI/mL)	2.7	0.8-24.3
Anti thyroglobulin Ab (IU/ml)	<10	0-115
WBC x $10^3/\mu$ L	14.8	6.0-16.0
RBC x $10^6/\mu$ L	6.8	3.9-5.1
Hgb g/dL	10.6	11.1-14.1
Hct %	35.3 %	30.0-38.0
MCV fl	51.7	72.0-84.0
MCH pg	15.5	25.0-29.0
RDW-CV %	21.0	11.6-14.5
Platelet x $10^3/\mu$ L	619	200-550
Absolute neutrophil count (ANC) x $10^3/\mu$ L	7.8	1.0-7.0
Lymphocyte x $10^3/\mu$ L	5.2	3.5-11.0
Monocyte x $10^3/\mu$ L	1.5	0.2-1.0
Urea (mmol/L)	1.7	0.7-4.6
Creatinine (mmol/L)	22	15-37

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Table 1. Laboratory results

Investigation	Result	Reference Range
Sodium (mmol/L)	135	135-145
Potassium (mmol/L)	4.5	4.1-4.7
Bicarbonate (mmol/L)	7.0	24.0-30.0
Calcium (mmol/L)	2.65	2.17-2.64
Glucose (mmol/L)	32.2	3.3-5.5
Anti transglutaminase IgA Ab (U/mL)	<0.10	<4 (4.0-10.0 weak positive; >10.0 positive)
Anti transglutaminase IgG Ab (U/mL)	Negative	--
Anti GAD Ab (IU/mL)	34.9	<5
PCR Assays for SARS-CoV-2	Positive	Negative
RdRp - gene CT	15.24	Positive for SARS-CoV-2
E- gene CT	16.07	Positive for SARS-CoV-2

The glycosylated hemoglobin level was 8.5 %. He had both ketonuria and glucosuria. The fasting C-peptide and insulin levels were low. Management with isotonic fluids and intravenous insulin therapy was initiated and the patient was transferred to the pediatric intensive care unit. Serum electrolytes were closely monitored. DKA correction was achieved in approximately 10 hours, after initiating the treatment. On the second day he recovered from lethargic condition, and the general condition gradually improved. On the third day, breast feeding was restarted with 5-6 daily feeds and two fruits /vegetables snacks, and intravenous insulin (IVF) was replaced by subcutaneous insulin [Levemir (Detemir) as basal insulin and Humalog

(Lispro) as prandial insulin]. Blood glucose was regularly monitored to adjust his blood glucose between 8 and 12 mmol/L (144 mg/dL- 216 ng/dL). Five days after the hospital admission, he was discharged with a diagnosis of newly-onset type 1 diabetes mellitus and concomitant COVID-19. Our next plan is to start insulin pump therapy, after further stabilisation and completion of parents 'diabetes education.

A written informed consent was obtained from the patient' parents for their blood collection and genetic analysis. The ethical committee of Hamad General Hospital (HGH) approved the publication of our case report.

Discussion

DKA is a metabolic disorder caused by the absolute or relative deficit of insulin associated with a concomitant rise in counterregulatory hormones (5). DKA is biochemically defined as a venous pH <7.3 or serum bicarbonate concentration <15 mmol/L, serum glucose concentration >11 mmol/L (>200 mg/dL) together with ketonemia, glucosuria, and ketonuria (6).

DKA is more prevalent in children less than 5 years of age (5). The symptoms are often nonspecific and there are many diseases that mimic the presentation. Some patients present with abdominal pain and vomiting. In the presence of cerebral oedema, consciousness can be altered. Hyperglycaemia results from increased hepatic and renal glucose production and impaired peripheral glucose utilisation which leads to osmotic diuresis and electrolyte imbalance. Mainstays of treatment are correction of hypovolemia and hyperglycaemia, rapid administration of insulin, and electrolyte management. Predictors of mortality are comorbidities, severe acidemia at presentation (arterial blood pH < 7.0), development of coma, or fever. The rate of mortality is 23.6% (7).

Infections are frequently seen as the most common precipitating factor of DKA. It is commonly admitted that certain viral diseases can trigger autoimmune type 1 diabetes in genetically susceptible patients, or even produce fulminant diabetes from mass collapse of β -cells (8,9). Serological evidence of infection and isolation of viruses from the pancreas have been reported in a few cases of recently diagnosed diabetes (8,9). Our baby resulted symptomatic and positive for COVID-19.

The interactions between SARS-CoV-2 infection and the renin-angiotensin-aldosterone system (RAAS) might provide an additional mechanism into the pathophysiology of DKA (10). The localization of angiotensin-converting enzyme 2 (ACE2), in the endocrine part of the pancreas suggests that SARS coronavirus enters islets using ACE2 as its receptor and may damage islets causing acute insulin dependent diabetes mellitus (11).

Substantially, SARS-CoV-2 enter as first into pancreatic islet cells and may directly aggravate β -cell injury (12). Secondly, the ACE2 downregulation, af-

ter viral entry, can lead to unopposed angiotensin II, which may impede insulin secretion (13). Although, these 2 factors might have contributed to the acute worsening of pancreatic β -cell function and precipitated DKA in our infant, the mechanisms linked to the development of dysglycemia remain still uncertain.

The relationship between SARS-CoV-2 and RAAS have also clinical implications for the management of DKA. Excessive fluid resuscitation may potentiate acute respiratory distress syndrome as angiotensin II increases pulmonary vascular permeability and worsens damage to lung parenchyma (14). Furthermore, angiotensin II stimulates aldosterone secretion, potentiating the risk of hypokalemia, which may necessitate more potassium supplementation to continue intravenous insulin (IVF) to suppress ketogenesis. Our infant had mild hypokalemia that was easily corrected by adding K to the IVF.

Although a consistent haematological pattern of characteristic laboratory findings has not yet been identified in children with confirmed COVID-19, the following abnormalities have been reported: lymphopenia, increased levels of liver and muscle enzymes, increased LDH, myoglobin and creatine kinase isoenzyme levels, elevated C- Reactive Protein (CRP), erythrocyte sedimentation rate and procalcitonin level. Our infant had neutrophilia, mild monocytosis and thrombocytosis, but CRP and procalcitonin were not elevated. While the most common pattern of coagulopathy observed in patients hospitalized with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels, our infant had only a mild increase of D-dimer and a high platelet count.

In conclusions, from a diabetologist's point of view, although the question remains open regarding COVID-19 and risk of new-onset diabetes, the case reported herein document an unique initial presentation of DKA in an infant with concomitant COVID-19. To address these issues, an international group of leading diabetes researchers participating in the CovidDIAB Project have established a global registry of patients with COVID-19-related diabetes (covid diab.e-dendrite.com) (15).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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