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Case Report
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A Case of Newly Onset Diabetic Ketoacidosis Following COVID-19 Infection

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Abstract

We report a case of an 8-year-6-month-old girl who was diagnosed with COVID-19 infection more than 2 months ago. After recovery, she developed polyuria, polydipsia, polyphagia, and weight loss. Her blood glucose level was 17.5 mmol/l, and fasting C-peptide was significantly reduced. Blood ketones, urine ketones, serum anti-glutamic acid decarboxylase antibodies, and anti-insulinoma associated antigen-2 antibodies were positive, and she was diagnosed with type 1 diabetes mellitus. After fluid replacement and insulin treatment, the ketosis was corrected, and blood glucose was stabilized. COVID-19 infection may act as an initiating factor for autoimmune destruction of pancreatic beta cells, directly or indirectly impairing the function of synthesizing insulin, resulting in type 1 diabetes mellitus.

Keywords: COVID-19 infection; Children; Diabetes mellitus; Ketosis-prone diabetes mellitus

Introduction

Since December 2019, the outbreak of the novel coronavirus (SARS-CoV-2), also known as COVID-19, has caused a global pandemic. It is the second coronavirus to cause a major outbreak in humans, following the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003, with an 82% genetic similarity between the two viruses [1]. While the accelerated development and distribution of COVID-19 vaccines have significantly reduced the incidence and mortality rates, the number of newly diagnosed Type 1 Diabetes (T1DM) cases has increased during the COVID-19 pandemic [2]. However, there are relatively few reports on children developing T1DM after COVID-19 infection. This article reports on a case of newly diagnosed T1DM with ketosis in an 8-year-and-6-month-old girl after recovering from COVID-19 infection. It discusses the correlation between T1DM and COVID-19 infection and analyzes how the immune and inflammatory responses triggered by COVID-19 infection may act as a trigger for the onset of diabetes.

Case Presentation

The patient, an 8-year-6-month-old girl, was admitted to the hospital on March 12th, 2023 due to "polyuria, polydipsia, and polyphagia with weight loss for over 2 months". She had been experiencing polyuria for over 2 months, urinating 3 to 4 times during the day and 2 to 4 times during the night. She also had increased thirst, drinking approximately 1 liter of water per day, and an increased appetite, leading to a weight loss of 10 kg in the past 2 months. She did not have any headaches, dizziness, abdominal pain, diarrhea, coma, or excessive sleepiness. She sought medical attention at a local hospital where her blood glucose was measured at 17.5 mmol/L. She was admitted to our hospital for further diagnosis and treatment for diabetes.

The patient had a history of COVID-19 infection, confirmed by positive COVID-19 RNA test results after presenting with fever and cough on December 25th, 2022. She was prescribed antipyretics, and her fever returned to normal on the third day of treatment. She was also prescribed cough syrup, which improved her cough and sputum production. Her chest X-ray and blood glucose tests were not completed during this period. The patient had received two doses of the COVID-19 vaccine: The first dose (Sinovac) on November 27th, 2021, and the second dose (Sinovac) on December 28th, 2021.

Personal history: The patient is a G1P1 full-term cesarean section with a birth weight of 3.5 kg.

Family history: Both parents are healthy, but the patient's grandmother has had type 2 diabetes for 5 years and is able to control her blood sugar with insulin and oral hypoglycemic agents. On admission, the patient was 144 cm tall and weighed 32.5 kg. The patient was alert, with no obvious dry lips, elastic skin, and no sunken eye sockets. There were no abnormalities found in the

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examination of the cardiovascular, respiratory, or nervous systems.

Auxiliary examination: Arterial blood gas and lactate: Lactate 1.0 mmol/L; pH 7.33; pCO_2 35.1 mmHg; pO2 82.4 mmHg; bicarbonate concentration 17.9 mmol/L; actual base excess - 6.8 mmol/L; anion gap 26.39. Blood glucose 17.4 mmol/l; serum β-hydroxybutyrate: 5.470 (0.02-0.27) mmol/L. Glycosylated hemoglobin A1c 15.1% (4.2-6.2%). Fasting C-peptide 0.21 (0.78-5.19) ng/mL; fasting insulin 6.1 (2.6-11.8) mIU/L. Serum anti-GAD antibody assay: >280.00 IU/ml; anti-islet cell antibody assay: 36.50 COI. Liver and kidney electrolytes: potassium 4.29 mmol/L, sodium 133 mmol/L, chloride 93 mmol/L, COVID-19 serum IgG antibody positive, COVID-19 serum IgM antibody negative. Urine routine: Urine glucose 4+ (111) mmol/L; urine ketone 3+ (7.4) mmol/L; urine protein and red blood cell count negative. Urine microalbumin assay normal. Thyroid function test, immunoglobulin IgG, IgM, IgA assay, cortisol assay (8AM), adrenocorticotropic hormone assay (8AM), and insulin-like growth factor assay all normal. Bilateral kidney ultrasound: Right kidney cyst (0.8 cm × 0.6 cm).

The diagnosis of type 1 diabetes with ketosis is definite in the child.

After admission, the patient was put under electrocardiogram monitoring and blood sugar monitoring. Immediately, 500 ml of normal saline was administered for fluid replacement. When blood sugar levels gradually decreased, a basal insulin pump dose and a high dose of subcutaneous injection before three meals were given. After correcting the ketosis and stabilizing blood sugar levels, the treatment was changed to a high dose of insulin injection before three meals and a long-acting insulin injection before bedtime. Diabetes education was provided, and blood sugar levels before meals fluctuated between 5 mmol/l to 7 mmol/l, and after meals fluctuated between 7 mmol/l to 10 mmol/l. The patient was discharged after achieving stable blood sugar levels. A follow-up visits half a month after discharge showed good blood sugar control in the patient.

Discussion

During the COVID-19 pandemic, there has been an increase in the number of newly diagnosed cases of Type 1 Diabetes (T1DM) [2-4]. According to data from the Centers for Disease Control and Prevention in the United States, adolescents under the age of 18 who contract COVID-19 are 2.6 times more likely to develop new-onset T1DM within 30 days compared to their peers [5]. Studies have also shown that the risk of being diagnosed with diabetes within 1 to 5 months after a COVID-19 diagnosis is nearly twice as high as in healthy individuals [6], and a follow-up study of up to one year on 180,000 COVID-19 recovered patients found a 40% increased risk of developing new-onset diabetes [7,8]. This article explores the correlation between type 1 diabetes and COVID-19 infection and emphasizes that the immune and inflammatory responses after coronavirus infection may serve as triggering factors for the onset of new diabetes.

T cells mediate organ-specific immune damage, which is an important factor in type 1 diabetes. Selective autoimmune destruction of beta cells leads to a lack of insulin secretion and disease. The etiology may be due to the interaction of genetic susceptibility factors and environmental factors resulting in immune dysregulation. Loss of immune tolerance in pancreatic beta cells leads to immune attack, which triggers autoimmune diabetes [9]. Genetic susceptibility factors include human leukocyte antigen, variable tandem repeat sequences in insulin genes, and cytotoxic T lymphocyte antigens. Environmental factors such as viral infections, dietary components, and chemical toxins, etc. Viral infections may act as the initiating factor of pancreatic beta cell autoimmune attack [10]. Currently, human viruses that are generally believed to be associated with type 1 diabetes include Coxsackie B virus, rubella virus, mumps virus, cytomegalovirus, EB virus, varicella-zoster virus, retroviruses, and rotaviruses, etc. [11].

There is a bidirectional relationship between COVID-19 and diabetes [5,7]. On one hand, diabetes is an important risk factor for severe COVID-19 and an independent predictor of poor prognosis in COVID-19 patients. On the other hand, COVID-19 can induce and exacerbate diabetes, with an increased number of new cases of type 1 diabetes observed in COVID-19 patients. In addition to directly inducing diabetes, COVID-19 infection can also lead to Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS) in diabetic patients, worsening their condition. This suggests that both direct and indirect factors caused by COVID-19 infection play important roles in the development of diabetes [8,12].

The SARS-CoV-2 virus has three structural proteins outside its envelope, namely Spike (S) protein, Envelope (E) protein, and Membrane (M) protein, with S protein being the key factor that mediates the virus's infection of target cells. The S protein is a homotrimer, and its extracellular domain can be divided into two subunits based on their functions, namely S1 and S2. The S1 subunit is mainly responsible for recognizing and binding to the receptor Angiotensin-Converting Enzyme 2 (ACE2) [13]. ACE2 is a key enzyme in the Renin-Angiotensin-Aldosterone System (RAAS). It catalyzes the conversion of angiotensin II to angiotensin [14]. ACE2 was initially reported to be expressed on the surface of respiratory epithelial cells, but subsequent studies found that it is highly expressed in other tissues, such as the intestine, kidney, cardiovascular system, and pancreas, including the surface of pancreatic islet cells [6]. It is the entry point for the SARS-CoV-2 virus, and its invasion of respiratory epithelial cells and other target cells involves binding with ACE-2. Increased expression of ACE2 facilitates more effective cell binding and entry. The possible implications of these interactions are twofold. Firstly, SARS-CoV-2 entering pancreatic beta cells directly induces a cytopathic effect leading to beta cell damage and the occurrence of diabetes. By binding with the specific receptor on the surface of beta cells, the virus invades and replicates within the cells, causing an increase in membrane permeability and impairing the function of beta cells to synthesize insulin [15]. Secondly, it induces cell lysis and directly destroys pancreatic beta cells. These two factors may lead to the deterioration of pancreatic beta cell function and the onset of diabetes. The coronavirus-mediated damage to pancreatic beta cells does not seem to be a new phenomenon, as evidenced by the experience of the previous SARS coronavirus outbreak [7].

The immune mechanism plays an important role in the development of type 1 diabetes. Cells infected with the novel coronavirus undergo apoptosis or necrosis, triggering an inflammatory response characterized by the activation of proinflammatory cytokines or chemokines, which leads to the recruitment of inflammatory cells. CD4+ T helper type 1 (Th1) cells regulate antigen presentation and immune responses to intracellular pathogens (such as coronaviruses) by interfering with Interferon-Gamma (IFN-γ) production. Th17 cells induce the recruitment of neutrophils and macrophages by producing Interleukin-17 (IL-17), IL-21, and IL-22. Novel coronavirus infection results in the apoptosis of circulating

immune cells, leading to a reduction in lymphocytes (CD3+, CD4+, and CD8+ T cells) and the secretion of large amounts of inflammatory cytokines, which is called a "cytokine storm". In fact, the circulating levels of cytokines (such as IL-6 and TNF-α) involved in the cytokine storm syndrome are elevated and may cause excessive inflammation in novel coronavirus infection, leading to multiple organ failure, loss of immune tolerance of pancreatic β-cells, and ultimately triggering autoimmune diabetes. It can be said that immune-mediated type 1 diabetes is caused by selective autoimmune destruction of pancreatic β-cells, leading to insulin secretion deficiency. The inflammatory cytokine IL-6 can also directly act on pancreatic cells, not only impairing the function of insulin secretion by pancreatic β-cells but also inducing their apoptosis. Therefore, in addition to the pancreatic and insulin damage caused by direct novel coronavirus infection, the critical inflammatory cytokine IL-6 induced by novel coronavirus infection can also cause or exacerbate diabetes by reducing insulin release and enhancing insulin resistance in peripheral tissues [16-23].

In addition, the inflammatory cells triggered by the new coronavirus infection not only infiltrate the lungs and cause lung damage and Acute Respiratory Distress Syndrome (ARDS), but also affect skeletal muscle and liver function. These two organs are responsible for insulin-mediated glucose uptake and gluconeogenesis, and inflammatory-induced functional impairments may lead to hyperinsulinemia and hyperglycemia [24,25].

In summary, COVID-19 infection may act as an initiating factor for autoimmune beta-cell damage, causing direct or indirect injury to pancreatic cells and loss of insulin secretion capacity after entering the cells through the ACE-2 receptor. The virus-mediated release of chemokines and cytokines from immune reactions can affect pancreatic cells, causing loss of immune tolerance and inducing the occurrence of autoimmune diabetes. Immune reactions may further impair the ability of the liver, muscles, and other peripheral organs to uptake glucose, thereby further causing or exacerbating diabetes. This also reminds us to strengthen the prevention of COVID-19, especially to pay attention to diabetes symptoms in children infected with COVID-19, including thirst, increased urination, weight loss, nausea, vomiting, and lethargy, and to timely receive blood glucose testing to detect diabetes in a timely manner.

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