CASE REPORT

Familial clustering of type 1 diabetes onset induced by COVID-19: case report

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Abstract

Type 1 diabetes (T1D) is a complex disorder with a genetic component that affects families due to heritable factors, such as polymorphisms in the human leukocyte antigen (HLA) region, as well as environmental triggers. Recent evidence suggests that viral infections, particularly coronavirus disease 2019 (COVID-19), may increase the risk of developing T1D. This case report presents a 24-year-old woman and her siblings who developed T1D a few months after recovering from COVID-19. The patient presented with acute hyperglycaemia, markedly elevated HbA1c levels, and glutamic acid decarboxylase 65 (GAD-65) autoantibodies indicating an autoimmunity. This case suggests that the COVID-19 pandemic may have accelerated autoimmune destruction of pancreatic β cells and demonstrates the urgent need to implement genetic counselling and autoantibody screening in individuals at risk. The reports highlight the need for further studies to explore the association between viral infection and T1D pathology on one hand, and public health measures for the prevention of COVID-19 on the other hand.

Keywords: COVID-19, Type 1 diabetes, Familial.

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Introduction

Familial clustering of type 1 diabetes (T1D) occurs at a rate higher than that expected by chance alone, and family members of patients with T1D exhibit significantly higher risks of developing the disorder than the general population. This implies that the aetiology of T1D may have both genetic and environmental facets.[1] Relatives of patients with T1D are diagnosed at a higher rate than the general population. The familial clustering of T1D is affected to a substantial degree by polymorphism of the human leukocyte antigen (HLA) region on 6p21.1 The lifetime risk of developing type 1 diabetes among siblings of affected individuals is estimated to be approximately 3%–8%, meaning that about 3 to 8 out of every 100 siblings may develop the disease during their lifetime (equivalent to roughly 1 in 35 to 1 in 12 siblings), which further indicates that T1D is a multi-factorial, heritable disorder. This ratio is utilized in risk modelling, with those loci being constitutive ratios to overall family risk.[2]

Emerging evidence suggests that infection with coronavirus disease 2019 (COVID-19) is associated with an increased risk of subsequent development of diabetes, particularly within the first few months after acute infection.[3] Many suppressive mediators, such as cytokines, can also induce changes to T1D developing characteristics that are harmful to the pancreas as well as insulin resistance.[4]

However, the mechanisms that correlate these two contributors to the development of T1D are often not discussed.[5] The role of COVID-19 in triggering the onset of T1D and the familial aggregation characteristics of this disease are inexhaustible subjects of investigation, and future studies are expected to shed light on prognosis considering the relationship between these diseases.

In this context, we present a familial case in which four siblings developed type 1 diabetes within months after confirmed COVID-19 infection, aiming to highlight the possible interaction between genetic susceptibility and viral triggers in the pathogenesis of autoimmune diabetes.

Case Report

We report the case of a 24-year-old female patient who presented with her mother and five siblings on January 7, 2024, to the emergency department (ED) at King Saud University Medical City, Riyadh, Kingdom of Saudi Arabia, with symptoms of fever, loss of sense of smell, fatigue, and dyspnoea. All family members were diagnosed with coronavirus disease 2019 (COVID-19) on the day of presentation to the ED, received appropriate treatment, and were discharged with normal blood glucose levels. There was no history of parental consanguinity.

Subsequently, three siblings of the patient were diagnosed with T1D between February and May 2024 at ages 7, 9, and 12 years, after presenting to the ED with diabetic ketoacidosis. The familial clustering of type 1 diabetes is illustrated in Figure 1.

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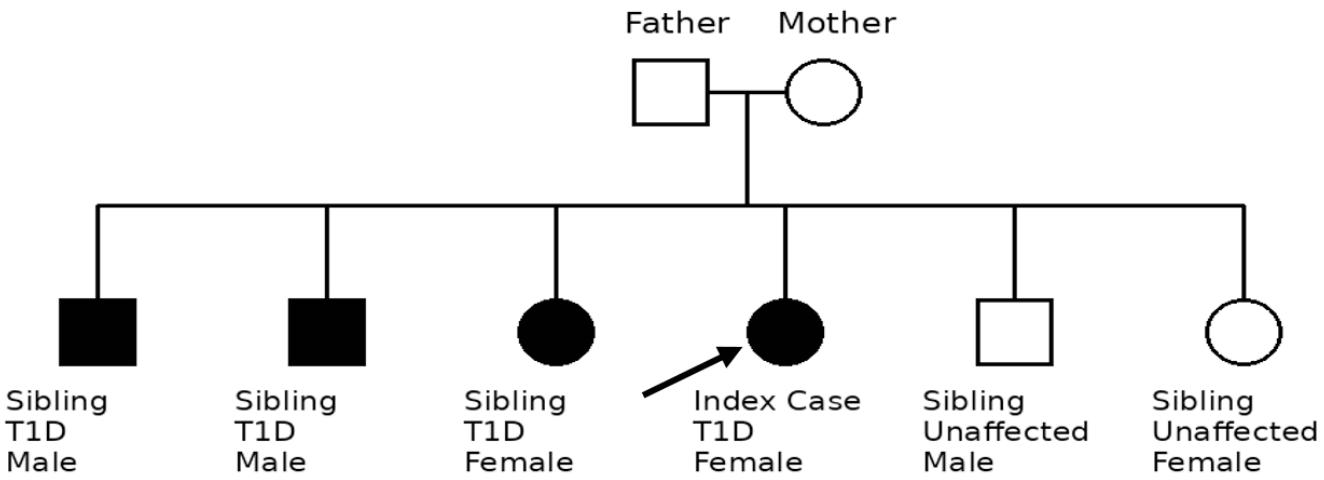

Figure: Family pedigree illustrating clustering of type 1 diabetes among siblings following COVID-19 infection. Squares represent males and circles represent females. Shaded symbols indicate individuals diagnosed with type 1 diabetes. The arrow denotes the index case.

Further, in June 2024, the patient developed acute polyuria, polydipsia, fatigue, nausea, and vomiting. T1D was diagnosed in the ED based on clinical presentation and laboratory findings. The level of glycaemia was 380 mg/dL (normal 70–140 mg/dL) (21.1 mmol/L) with no significant ketosis (0.5 mmol/L) (normal <0.6 mmol/L) and a normal bicarbonate level of 24 mmol/L (normal 22–29 mmol/L), HbA1c level of 11.2% (normal <5.7%) (15.2 mmol/mol), and body mass index of 23.5 kg/m^2 were noted at the time of diagnosis.

No metabolic comorbidities were observed in the patient (no signs of hypertension, c reactive protein levels < 0.5 mg/L (normal <5 mg/L), high-density lipoprotein levels 35 mg/dL (normal >40 mg/dL), low-density lipoprotein levels 110 mg/dL (normal <100 mg/dL), serum triglyceride levels 127 mg/dL (normal <150 mg/dL), normal liver enzymes and ferritin levels, and no signs of fatty liver on ultrasound).

C-peptide levels were reduced to 0.16 ng/mL (normal 0.9–1.8 ng/mL), as measured in a fasting (baseline) sample. Insulin levels were 0.40 mU/mL (normal 2–25 mU/mL); thyroid stimulating hormone 2.25 mIU/L (normal 0.4–4.0 mIU/L); free T4 18.7 pmol/L (normal 12–22 pmol/L); thyroglobulin antibody was 7.55 IU/mL (normal <115 IU/mL), and TPO antibody was 14.24 IU/mL (normal <34 IU/mL); and creatinine 76 µmol/L (normal 60–110 µmol/L).

Thereafter, glutamic acid decarboxylase 65 (GAD-65) enzyme assays were performed, and GAD-65 autoantibodies were found to be present (162.6 IU/mL) (normal <10 IU/mL), indicative of type 1 immune-diabetes, while islet antigen-2 autoantibodies (IA2A) and zinc transporter 8 autoantibodies (ZnT8A) were absent. An indirect evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was noted (Elecsys® Anti-SARS-CoV-2 assay, Roche Diagnostics International Ltd., Rotkreuz, Switzerland), indicating that the patient had been infected with COVID-19 prior to diagnosis with T1D.

The patient required immediate administration of insulin. After discharge from the ED, the patient received follow-up care at the University Family Medicine Center, King Saud University Medical City, Riyadh, Kingdom of Saudi Arabia, and several months later, with comprehensive diabetes care, her HbA1c dropped to 7.3%.

Discussion

This is a unique case, as four siblings in a family were diagnosed with T1D within several months following COVID-19. This case supports the potential etiological role of viral infections, particularly COVID-19, in triggering autoimmune diseases such as T1D.[6] However, T1D has a genetic component and is known to aggregate in families, with siblings of affected individuals having a higher risk of developing T1D compared with the general population.[7] The familial risk ratio for T1D is approximately 15, indicating that if one child in a family is diagnosed with T1D, the lifetime risk for other siblings is more than 15 times higher than that of a non-diabetic population.[8] This case highlights the need for conducting genetic tests, counselling of relatives, and screening for disease-associated alleles.

Viral infections have long been thought to act as instigating factors in the development of autoimmune

disorders such as T1D. A study in Finland reported an increase in the rate of diagnosis of T1D during the period of COVID-19 pandemic, reaching 61.0 cases per 100,000 person-years.[8]

Approximately 5–10% of autoimmune T1D cases occur due to the pathogenicity of self-immune β-cell lethality. Diagnosis of the autoimmune process in patients includes the presence of circulating GAD antibodies (GAD65), IA 2 glycoprotein, and Zn transporter mRNA.[8]

It has been proposed that COVID-19 can damage or destroy pancreatic β cells, which may, in the long run, result in T1D development.[9] The SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2) receptors of the pancreas, initiating an inflammatory process that may promote the onset of T1D in such patients.[10]

This case emphasizes the importance of family history-taking, screening for autoantibodies at an early stage, and attentively monitoring family members who are at risk of developing autoimmune diseases.

Conclusion

This report details four siblings who manifested type 1 diabetes shortly after confirmed COVID-19 infection. Three cases exhibited diabetic ketoacidosis, while the index case demonstrated positive GAD-65 antibodies and significantly diminished C-peptide levels, thereby confirming autoimmune β-cell failure. The close temporal clustering following COVID-19 infection within a single family indicates a possible viral trigger in genetically predisposed individuals and advocates for early post-infection screening for hyperglycaemia and diabetes-related autoantibodies among at-risk relatives.

Informed Consent: was obtained from all subjects involved in the study and was taken prior to the writing of the manuscript and its publication. Written informed consent was provided by the patients to publish this report.

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NAA: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.