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Case Report

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Monogenic Diabetes in a Child with Cystic Fibrosis: A Case Report and Review of the Literature

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Abbreviations: BMI, body mass index;CF, cystic fibrosis;CFRD, cystic fibrosis–related diabetes;GCK, glucokinase;HbA1c, glycated hemoglobin A1c;MODY, maturity onset diabetes of the young;OGTT, oral glucose tolerance test;T1D, type 1 diabetes;T2D, type 2 diabetes.

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Abstract

Cystic fibrosis–related diabetes (CFRD) is associated with worsening pulmonary function, lower body mass index, increased infection frequency, and earlier mortality. While the incidence of CFRD is rising, its development in patients under the age of 10 years is uncommon.

We present a 9-year-old girl with cystic fibrosis (CF) who presented with a 5-year history of nonprogressive hyperglycemia, demonstrated by abnormal oral glucose tolerance tests, glycated hemoglobin A1c (HbA1c) levels consistently >6.5%, and negative pancreatic autoantibodies. Subsequent genetic testing revealed a pathogenic heterozygous recessive mutation in the *GCK* gene at c.667G>A (p.Gly223Ser), consistent with a diagnosis of GCK-MODY.

Significant dysglycemia in young children with CF should raise suspicion for alternative etiologies of diabetes and warrants further investigation. The clinical impact of underlying monogenic diabetes in patients with CF is unclear, and close follow-up is warranted. This case also offers unique insight on the impact of hyperglycemia in the absence of insulin deficiency on CF-specific outcomes.

Key Words: cystic fibrosis, cystic fibrosis–related diabetes, maturity onset diabetes of youth, monogenic diabetes, GCK-MODY

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Over the past several decades, the prevalence of nonpulmonary complications of cystic fibrosis (CF) has increased, particularly CF-related diabetes (CFRD). CFRD affects ~2% of children, ~20% of adolescents and 35% to 50% of adults with CF and is associated with worse outcomes, including decreased pulmonary function, lower body mass index (BMI), and earlier mortality [1-4]. Although the pathogenesis of CFRD is still not fully understood, the etiology of CFRD is thought to be multifactorial, related to islet cell dysfunction and β-cell loss from pancreatic exocrine disease, increased insulin resistance from inflammatory cytokines and stress hormones, and possibly a direct effect of defective CFTR protein on β-cell function [1]. Abnormal glucose tolerance is relatively common in children with CF under the age of 10 years and is associated with a higher risk of progression to early onset diabetes [5]. However, while 2-hour oral glucose tolerance test (OGTT) blood glucose values >200 mg/dL are not infrequently seen in pediatric patients with CF, fasting hyperglycemia and elevated glycated hemoglobin A1c (HbA1c) levels are atypical [5].

Current guidelines recommend annual screening for CFRD with an OGTT beginning at age 10 years [1]. The development of CFRD prior to puberty is uncommon; therefore, hyperglycemia in very young children with CF should raise clinical suspicion for alternative etiologies of diabetes.

1. Case Report

A 9-year-old girl with CF (homozygous delF508) and pancreatic insufficiency presented to our CF endocrinology clinic due to concern for CFRD. Since the age of 4 years, HbA1c levels drawn during routine annual screening were elevated but remained remarkably stable, ranging 6.8% to 7.1% (Table 1). An OGTT performed at age 7 revealed impaired fasting glucose (100-125 mg/dL), indeterminate glycemia (1-hour glucose >200 mg/dL), and impaired glucose tolerance (2-hour glucose 140-199 mg/dL) (Table 1). She had no history of weight loss, polyuria, polydipsia, changes in appetite, or chronic glucocorticoid treatment. Her BMI and forced expiratory volume in 1 second (FEV1) ranged in the 80th to 90th and 89th to 105th percentiles, respectively, over the previous several years. She was hospitalized once for a CF exacerbation in 2017. There was no known family history of diabetes. Examination was notable for absence of acanthosis nigricans. Further testing after the initial endocrinology visit revealed negative pancreatic autoantibodies, and a repeat OGTT showed abnormal glucose tolerance very similar to her test results from 2 years prior (Table 1).

Given her very young age at presentation and the stable degree of glucose intolerance over the preceding 5 years, we suspected an alternative cause for her dysglycemia other than CFRD. Type 1 diabetes (T1D) was unlikely given the negative pancreatic autoantibodies and nonprogressive clinical course. Type 2 diabetes (T2D) was also a consideration; however, her lack of family history, nonobese habitus, lack of physical signs of insulin resistance, and very young age at presentation argued against this diagnosis. A well-studied clinical prediction model determined her maturity onset diabetes of the young (MODY) risk to be 75.5% [6]. Sequencing and deletion/duplication analysis of known genes associated with monogenic diabetes in a commercial genetics laboratory (https://dnatesting.uchicago.edu/tests/mody-panel) revealed a pathogenic heterozygous recessive mutation in the *GCK* gene at c.667G>A, leading to amino acid change p.Gly223Ser, consistent with a diagnosis of GCK-MODY.

Table 1. Laboratory Data

	7/30/14 7.1 yrs	5/1/17 6.8 yrs	5/5/17 6.8 yrs	8/21/18 8.1 yrs	8/13/19 9.1 yrs	9/4/19* 9.2 yrs	10/1/19 9.3 yrs
HbA1c	7.1%	6.9%		6.9%	6.8%	6.8%	
Insulin level (IU/mL)						15.8	
OGTT							
-Fasting glucose			121				124
-Fasting insulin							10.6
-1-hour glucose			217				210
-1-hour insulin							80.3
-2-hour glucose			140				121
-2-hour insulin							21.2
GAD antibody (IU/mL)						<5	
IA-2 antibody (unit/mL)						<5.4	
Insulin antibody (unit/mL)						<0.4	

Abbreviations: HbA1c, glycated hemoglobin A1c; OGTT, oral glucose tolerance test.
*date of first endocrinology evaluation.

2. Discussion

Maturity onset diabetes of the young (MODY), a form of monogenic diabetes, is due to autosomal dominant mutations in genes involved in β-cell development and insulin secretion [7-9]. MODY is characterized by onset prior to 25 years of age, absence of pancreatic autoimmunity, and in some cases a strong family history of diabetes (≥3 consecutive generations), although de novo mutations are relatively common [7].

GCK-MODY is the most common cause of persistent, incidentally discovered hyperglycemia in the pediatric population, occurring in 1 in 1000 individuals [7]. The *GCK* gene is primarily expressed in the liver and pancreatic β-cells and encodes glucokinase, also known as the pancreatic β-cell glucose sensor [7-9]. In the liver, glucokinase plays a key role in storage of glucose in the form of glycogen [10]. In the pancreatic β-cell, glucokinase functions as the rate-limiting enzyme for glycolysis, and is required for ATP-mediated phosphorylation of glucose to form glucose-6-phosphate [7, 10-12]. There are more than 600 reported mutations in *GCK* [12]. Autosomal dominant heterozygous inactivating mutations in *GCK* result in decreased sensitivity of pancreatic β-cells and a raised threshold for glucose-stimulated insulin secretion [8, 9]. Patients with GCK-MODY typically present with mild, nonprogressive fasting hyperglycemia with HbA1c values ranging from 6% to 7.3% and relatively small increases in 2-hour OGTT glucose values [7-9]. Patients with GCK-MODY do not develop the microvascular or macrovascular complications typically associated with other forms of diabetes and therefore do not require regular glucose monitoring or pharmacologic treatment with insulin or oral hypoglycemic agents, apart from during pregnancy [7, 9]. In fact, patients with GCK-MODY treated with oral medications or insulin have higher rates of adverse events, particularly hypoglycemia [9].

Data regarding concurrent diagnosis of MODY in patients with CF are limited. Gan et al described a family with 3 siblings (ages 7, 12, and 16 years) presenting with pancreatic autoantibody-negative diabetes, 2 of whom had CF with genotypes typically associated with pancreatic sufficiency (delF508/R117H;IVS8-5T) [8]. Family history was notable for 3 successive generations of individuals diagnosed with T1D or T2D. Genetic testing revealed a heterozygous frameshift mutation in the *HNF1A* gene at c.404delA. All 3 siblings ultimately started sulfonylurea therapy, the targeted treatment for *HNF1A* mutations, which led to significant improvement in glycemic control. Hangul et al described an infant with CF (homozygous delF508) incidentally discovered to have persistent mild hyperglycemia since day-of-life 30 [9]. Low-dose insulin was started; however, subsequent genetic testing revealed a de novo heterozygous mutation in the *GCK* gene at c.1086_1090delCGACT p.D363RfsX94). Insulin was discontinued, and fasting glucose levels were monitored without intervention. Salzano et al recently described the management conundrums in a 6-year-old patient with CF, GCK-MODY, and mild hyperglycemia, electing to defer medical management of her mild hyperglycemia for the time being [13].

The diagnosis of MODY in children with CF may be more complicated than in other diabetes populations. The clinical prediction model used in this case was developed from logistical regression analysis of 1191 patients with MODY (n=594), T1D (n=278) or T2D (n=319) and utilized discriminating characteristics such as lower HbA1c value, family history of diabetes, female gender, age, lower BMI, and lack of insulin therapy or oral hypoglycemic agent use. However, this model does not specifically account for the fact that children with CF are at higher baseline risk for diabetes than those with T1D or T2D, and it has not been validated for use in patients with CFRD. Therefore, although helpful in raising the concern for underlying MODY, this clinical prediction tool likely does not have the same predictive value in this patient population and requires further study.

The presence of a *GCK* mutation in a patient with CF raises several important clinical concerns. Although the mild hyperglycemia caused by GCK-MODY typically does not require pharmacologic therapy, mild glycemic abnormalities in patients with CF have been associated with pulmonary decline and nutritional compromise [3, 7, 9, 14]. When plasma glucose levels exceed 140 mg/dL, glucose becomes detectable in airway surface liquid, providing an enriched medium for the proliferation of CF pathogens and impacting neutrophil chemotaxis and function [4, 14]. Although this mild hyperglycemia may not cause microvascular disease, whether it has other detrimental effects in patients with CF is unknown.

Additionally, although her current dysglycemia is likely due to her underlying *GCK* mutation, this patient may still be at risk for developing insulin deficiency from β-cell damage caused by her underlying CF and pancreatic disease. Therefore, close monitoring is warranted for evidence of worsening glycemic control that would suggest the development of CFRD on top of her monogenic diabetes. Although data are limited, annual OGTTs and HbA1c levels would be useful in this scenario, monitoring for a rise in the 2-hour glucose value to >200 mg/dL and/or a sustained increase in HbA1c above her prior baseline that would be suggestive of CFRD. The physiologic state of insulin resistance associated with puberty often coincides with progression to diabetes in patients with CF and abnormal

glucose tolerance. Puberty will therefore be a particular important period for monitoring our patient. However, as GCK-MODY is due to a defect in the set-point for glucose-stimulated insulin secretion and not an impaired ability to produce insulin (as is the case of other forms of MODY such as those associated with hepatic nuclear transcription factors or with pancreatic dysplasia), it is possible that the risk of significantly worsened dysglycemia and progression to diabetes during puberty may be less severe for our patient.

Insulin is the only recommended treatment for CFRD; however, insulin therapy in patients with noninsulinopenic forms of MODY, such as GCK-MODY, has been associated with worse outcomes due to an altered counter-regulatory response to hypoglycemia. If this patient's glycemic control and/or clinical status worsens, treatment with insulin may be necessary. However, insulin therapy in this clinical setting would likely require tailored glycemic targets, careful insulin titration, and close glucose monitoring using technology like continuous glucose monitors.

Finally, this case presents a unique opportunity to gain insight into the mechanism by which diabetes impacts CF. It is currently debated whether the detrimental effects of CFRD on nutritional status and pulmonary function are due to hyperglycemia itself or to insulin deficiency. This patient with GCK-MODY has hyperglycemia caused by the altered glycemic set-point from her mutation but normal insulin secretory capacity, thereby offering the opportunity to learn how isolated elevated glucose values without underlying insulin deficiency will impact her clinical status moving forward.

3. Conclusions

We describe an unusual case of MODY in a child with CF. While very young children can develop CFRD, this is uncommon and should prompt an evaluation for other forms of diabetes. This case illustrates current gaps in our knowledge of CFRD and presents an opportunity to learn about the impact of hyperglycemia, in the absence of insulin deficiency, on CF-specific outcomes.

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Additional Information

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References

1. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;**33**(12):2697-2708.
2. Cystic Fibrosis Foundation. 2017 Patient Registry Annual Data Report; 2018. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf. Accessed August 1, 2020.
3. Prentice BJ, Ooi CY, Strachan RE, et al. Early glucose abnormalities are associated with pulmonary inflammation in young children with cystic fibrosis. *J Cyst Fibros*. 2019;**18**(6):869-873.
4. Brennan AL, Gyi KM, Wood DM, et al. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. *J Cyst Fibros*. 2007;**6**(2):101-109.
5. Ode KL, Frohnert B, Laguna T, et al. Oral glucose tolerance testing in children with cystic fibrosis. *Pediatr Diabetes*. 2010;**11**(7):487-492.
6. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia*. 2012;**55**(5):1265-1272.
7. Hattersley AT, Greeley SAW, Polak M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2018;**19**:47-63.
8. Gan HW, Bhatt JM, Denvir L, Randell T, Sachdev P. Monogenic diabetes mellitus in cystic fibrosis. *Arch Dis Child*. 2019;**104**(9):887-889.
9. Hangül M, Erdoğan M, Hatipoğlu N, Köse M. Maturity-onset diabetes of the young: different diabetes in an infant with cystic fibrosis. *Pediatr Pulmonol*. 2020;**55**(5):E5-E7.
10. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med*. 2001;**345**(13):971-980.
11. Thanabalasingham G, Owen KR. Diagnosis and management of maturity onset diabetes of the young (MODY). *BMJ*. 2011;**343**:d6044.
12. Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. *Curr Diab Rep*. 2018;**18**(8):58.

13. Salzano G, Passanisi S, Lucanto MC, Costa S, Pajno GB, Lombardo F. GCK-MODY in a child with cystic fibrosis: the doubt of the treatment plan. *J Pediatr Endocrinol Metab*. 2020;**33**(10):1359-1362.

14. Hunt WR, Zughaier SM, Guentert DE, et al. Hyperglycemia impedes lung bacterial clearance in a murine model of cystic fibrosis-related diabetes. *Am J Physiol Lung Cell Mol Physiol*. 2014;**306**(1):L43-L49.