Pediatric Case Series of Cystic Fibrosis, Diabetes, and Islet Cell Autoimmunity

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Diabetes is the most common comorbidity in individuals with cystic fibrosis (CF). Among people with CF, the prevalence of CF-related diabetes (CFRD) is estimated to be 2% in children, 19% in adolescents, 40% in individuals in their 20s, and 45–50% in those ≥30 years of age (1). CFRD shares some aspects with type 1 diabetes in that it is primarily due to insulin deficiency, but it is distinguished from type 1 diabetes because of its insidious onset over years and the persistence of some insulin production long after diagnosis, which makes diabetic ketoacidosis (DKA) very rare in CFRD (2).

Routine screening for type 1 diabetes autoantibodies is not recommended for patients with CF and hyperglycemia (3). However, the following three cases illustrate certain instances that may warrant checking for type 1 diabetes autoantibodies (i.e., hyperglycemia before age 10, symptomatic presentation, and DKA; increasing insulin requirement; or presence of other autoimmune diseases or family history of autoimmune diseases in a CF patient).

Case Presentations

Patient 1

Patient 1 is a non-Hispanic white male with CF (genotype delta F508 homozygous), pancreatic insufficiency, and CF-related liver disease who presented at 16 years of age with polyuria, polydipsia, dry mouth, and weight loss of 5 kg over 3 months. His family history was positive for hypothyroidism in his father and CF in his sister and negative for diabetes. His height was 152 cm (<1st percentile), his weight was 41.6 kg (<1st percentile), and his BMI was 18.0 kg/m^2 (12th percentile). Physical examination showed normal mental status, no Kussmaul breathing, dry mucous membranes, and clubbing. Laboratory evaluation revealed fasting glucose of 350 mg/dL, pH 7.42, bicarbonate 24 mEq/L, blood urea nitrogen (BUN) 22 mg/dL, and creatinine 0.6 mg/dL. Urinalysis showed +3 glucose and +1 ketones. His C-peptide level was 1.1 ng/mL (normal range 1.1–4.4 ng/mL), and his A1C was >14%. Type 1 diabetes autoantibodies testing was positive for anti-GAD at 147 (normal range ≤25) and negative for islet cell antigen autoantibody 512 (IA-2), zinc transporter 8 (ZnT8), and insulin autoantibodies (IAAs).

He was started on insulin 0.8 units/kg/day (insulin glargine 16 units at night and insulin lispro with a carbohydrate ratio of 1 unit per 15 g carbohydrates, a sensitivity of 1 unit per 50 mg/dL, and a target blood glucose of 120 mg/dL). His current insulin requirement at the age of 23 years is 0.8–0.9 units/kg/day, and his A1C since diagnosis has ranged from 6.7 to 12.0%. He does not have other autoimmune diseases.

Patient 2

Patient 2 is patient 1's sister, a non-Hispanic white female with CF (genotype delta F508 homozygous) and

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pancreatic insufficiency. She was initially diagnosed with CFRD at 9 years of age when she had her first oral glucose tolerance test (OGTT) screening. At that time, she was asymptomatic with no weight loss, polyuria, or polydipsia. Her height was 123.5 cm (1st percentile), her weight was 27.4 kg (19th percentile), and her BMI was 18 kg/m^2 (69th percentile). Physical examination was unremarkable. Her OGTT showed a fasting glucose of 92 mg/dL and a 2-hour glucose of 209 mg/dL. Her C-peptide level was 7.1 ng/mL, and her A1C was 6.7%. Type 1 diabetes autoantibodies were negative at presentation. She was started on insulin at 0.4 units/kg/day (insulin glargine 5 units at night and insulin lispro with a carbohydrate ratio of 1 unit per 75 g carbohydrate, a correction factor of 1 unit per 150 mg/dL, and a target blood glucose of 150 mg/dL).

At the age of 14 years, because her insulin requirement was increasing and her A1C had increased from 6.9 to 11.2% over 18 months, type 1 diabetes autoantibodies were retested and found to be positive (anti-GAD 31, IA-2 52 [normal range ≤7], and ZnT8 0.955 [normal range ≤0.030]). Her treatment was intensified, and insulin was dosed at 1 unit/kg/day (insulin glargine 25 units at night and insulin lispro with a carbohydrate ratio of 1 unit per 16 g carbohydrate, a sensitivity of 1 unit per 35 mg/dL, and a target blood glucose of 100 mg/dL). Her current insulin dose at 16 years of age is 0.7 units/kg/day, and her A1C since diagnosis has ranged from 6.7 to 12.7%. No other autoimmune diseases were diagnosed.

Patient 3

Patient 3 is a biracial (non-Hispanic black, non-Hispanic white) female with CF (genotype 1 copy of delta F508 and 1 copy of delta I507), pancreatic insufficiency, and autoimmune thyroiditis with hypothyroidism, on thyroid hormone replacement. Hypothyroidism was diagnosed 4 months before her diabetes presentation. She presented at the age of 9 years with polyuria, polydipsia, fatigue, and weight loss of 4.5 kg over 3 months. Family history was positive for rheumatoid arthritis in her maternal grandmother and hypothyroidism on her mother's side and negative for diabetes. Her height was 147 cm (97th percentile), her weight was 26.3 kg (20th percentile), and her BMI was 12.2 kg/m^2 (<1st percentile). Physical examination revealed normal mental status and increased work of breathing consistent with Kussmaul breathing in addition to dry mucous membranes. Laboratory evaluation was consistent with DKA, with glucose 686 mg/dL, pH 7.06, bicarbonate 5 mEq/L, beta-hydroxybutyrate 5.4 mmol/L, BUN 15 mg/dL, and creatinine 0.7 mg/dL. Her C-peptide level was 0.1 ng/mL, and her A1C was >14%. Type 1 diabetes autoantibodies testing was positive (anti-GAD 192, IA-2 183, ZnT8 0.177, and IAAs 0.017). There were no concerns regarding cerebral edema.

She was treated with an insulin infusion of 0.1 units/kg/hour and then transitioned to a basal-bolus insulin regimen after DKA resolution with a dose of 0.8 units/kg/day (insulin glargine 10 units at night and insulin lispro with a carbohydrate ratio of 1 unit per 20 g carbohydrate, a sensitivity of 1 unit per 85 mg/dL, and a target blood glucose of 120 mg/dL). Her current insulin dose at the age of 11 years is 0.55 units/kg/day, and her A1C since diagnosis has ranged from 7.7 to 10.2%. The patient has switched from multiple daily injections to continuous subcutaneous insulin infusion (CSII). She reports improved satisfaction with CSII.

None of the three patients described above have developed microvascular complications (i.e., microalbuminuria or retinopathy), hypertension, or dyslipidemia, although their diabetes duration is only 4–7 years.

Questions

1. How common are positive type 1 diabetes autoantibodies in CF patients with hyperglycemia?
2. How can primary care providers (PCPs) play a role in diabetes screening in CF patients?
3. When should providers consider screening CF patients with hyperglycemia for diabetes autoantibodies (i.e., autoimmune type 1 diabetes)?
4. Why is it important to correctly diagnose the type of diabetes associated with CF?

Commentary

Here, we report three unique cases of CF with diabetes related to islet cell autoimmunity. Type 1 diabetes was suspected because of the severity of presentation (patient 1), increasing insulin requirement and family history of type 1 diabetes (patient 2), and DKA presentation and presence of autoimmune thyroid disease (patient 3). The third example (involving DKA) highlights the need to correctly identify the type of diabetes to prevent the morbidity and mortality associated with type 1 diabetes.

Annual screening for CFRD is recommended for CF patients who are ≥10 years of age. This test appears burdensome because it requires patients to fast and is time-consuming. PCPs can play an important role in advocating for CF patients to undergo an annual OGTT. PCPs should encourage those CF patients who are diagnosed with CFRD to adhere to their insulin regimen because of its benefits on nutrition and pulmonary function. For most patients with CFRD, the A1C goal is ≤7% to reduce the risk for microvascular complications.

Screening CF patients with hyperglycemia for type 1 diabetes autoantibodies is not routinely recommended. Data are conflicting on the frequency of islet cell autoimmunity in CF patients with diabetes. In the general population, 2% of individuals are positive for IA-2, GAD,

ZnT8, or IAAs (4). In type 1 diabetes, 55–98% of patients are positive for at least one of these autoantibodies (5). Few studies reported no increased rate of islet cell autoimmunity in CFRD patients (6–8). Gottlieb et al. (8) reported that the presence of autoantibodies associated with type 1 diabetes is no greater in CFRD than in the general population. In a sample of 76 CFRD patients with fasting hyperglycemia, only 5% had type 1 diabetes autoantibodies, including three subjects with antibodies to GAD and one subject with antibodies to IA-2. In contrast, more recently, Konrad at al. (9) reported that, in a cohort of 837 CFRD patients, 8.5% had positive type 1 diabetes antibodies (64% had IA-2 antibodies, 76% had islet cell antibodies [ICAs], 72% had GAD antibodies, and 83% had IAAs), indicating that the rate of islet cell autoimmunity in CFRD is higher than in the general population.

Our three cases illustrate specific circumstances in which screening for type 1 diabetes autoimmunity should be considered. CFRD is rare in prepubertal children (1). Also, CF patients are often asymptomatic at the time of diabetes diagnosis because CFRD is subtle and gradual in onset (2). When comparing CFRD patients with type 1 diabetes autoimmunity to those without autoimmunity, Konrad et al. (9) found that diabetes onset was earlier, insulin doses were higher, A1C was higher, and thyroid autoimmunity was more common in those with type 1 diabetes autoimmunity. Therefore, hyperglycemia before the age of 10 years, symptomatic presentation, DKA, increasing insulin requirement, the presence of other autoimmune diseases, or a family history of autoimmune diseases in CF patients should prompt a work up to rule out type 1 diabetes autoimmunity.

Treatment of CFRD is different from that of type 1 diabetes because the latter involves more intensive insulin dosing and glucose monitoring given the absolute insulin deficiency associated with it. In CFRD, insulin secretion is rarely totally absent. Therefore, patients usually require lower doses of insulin and rarely develop DKA. The rate of treatment complications such as severe hypoglycemia with coma and DKA are significantly higher in antibody-positive CFRD patients compared to those who are antibody negative (hypoglycemia with coma 8.0 vs. 1.4%, $P < 0.05$; DKA 9.3 vs. 0.9%, $P < 0.05$) (9).

Correctly diagnosing the type of diabetes in CF is important because it has an impact on diabetes progression, care, and treatment; it helps prevent the short-term complications associated with type 1 diabetes, especially DKA, with its worrisome complication of cerebral edema. It is also important for appropriate screening for long-term micro- and macrovascular complications given that the rate of these complications is higher in type 1 diabetes than in CFRD (10).

Clinical Pearls

- PCPs should ensure that CF patients undergo a yearly OGTT. For CF patients who develop diabetes, PCPs should encourage adherence to their insulin regimen and monitor whether they are meeting the A1C goal of ≤7%.
- Type 1 diabetes should be considered in CF patients with hyperglycemia when patients are prepubertal, symptomatic, in DKA, requiring high insulin doses, or have other autoimmune diseases or a family history of autoimmune diseases.
- Correct diagnosis allows for proper treatment and helps to prevent short- and long-term diabetes complications.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

Both authors researched data and co-wrote the manuscript. G.J.K. is the guarantor of this work and, as such, had full access to all data and takes responsibility for the integrity of the data and accuracy of the information presented.

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