Identifying and Managing Atypical Diabetes in Adults

INTRODUCTION

Autoimmune diabetes is a disorder that can develop at any age. Although it is classically thought of as a condition that emerges in childhood, close to one-half of all cases are diagnosed in adulthood. Although both childhood and adult-onset type 1 diabetes (T1D) are, by definition, autoimmune forms of beta-cell loss, they can present differently. Children with new-onset T1D are often acutely symptomatic, whereas adults with new-onset T1D have more indolent symptoms that are often initially confused with symptoms of type 2 diabetes (T2D). Table 1 describes the differences and similarities.

This handout discusses the different presentations of atypical diabetes in adults. Case examples are used to demonstrate how individuals with atypical symptoms are often initially misdiagnosed and how their treatment plans need to be adjusted once a correct diagnosis is made.

TABLE 1. Differences Between Child-Onset T1D, T2D, and Adult-Onset T1D

<table>
<thead>
<tr>
<th>Features at diagnosis</th>
<th>CHILDHOOD-ONSET T1D</th>
<th>T2D</th>
<th>ADULT-ONSET T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Childhood or adolescence</td>
<td>Adulthood</td>
<td>≥ 18 years</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>Generally negative; sometimes positive</td>
<td>Frequently positive</td>
<td>Generally negative; sometimes positive</td>
</tr>
<tr>
<td>Symptom onset</td>
<td>Acutely symptomatic</td>
<td>Often asymptomatic, sometimes symptomatic</td>
<td>Asymptomatic to markedly symptomatic</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Positive</td>
<td>Negative, although some have low levels of antibodies</td>
<td>Positive</td>
</tr>
<tr>
<td>C-peptide levels (over time)</td>
<td>Low to undetectable</td>
<td>High to low normal</td>
<td>Low to undetectable</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Normal or underweight as children; similar to the rest of the population as adults: one-third normal weight, one-third overweight, one-third obese</td>
<td>Generally overweight or obese</td>
<td>Similar to the rest of the population: one-third normal weight, one-third overweight, one-third obese</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Normal, although, as adults, can develop metabolic syndrome</td>
<td>Often with metabolic syndrome</td>
<td>Normal, although can have coexisting metabolic syndrome</td>
</tr>
<tr>
<td>Pancreas and insulin-related characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-cell function</td>
<td>No to minimal</td>
<td>Increased, normal, or decreased</td>
<td>No to minimal—often develops slowly over time</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Normal</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Depends on body weight; generally normal initially</td>
<td>Increased</td>
<td>Depends on body weight; increased if overweight or obese</td>
</tr>
<tr>
<td>Exogenous insulin requirement</td>
<td>At diagnosis</td>
<td>None or years after diagnosis</td>
<td>Usually &gt; 6 months after diagnosis</td>
</tr>
<tr>
<td>Risk of complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (hypoglycemia and DKA)</td>
<td>Increased</td>
<td>Mildly increased; hypoglycemia risk depends on therapy</td>
<td>Increased</td>
</tr>
<tr>
<td>Long-term (retinopathy, nephropathy, neuropathy)</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**WHAT’S IN A NAME?**

The very existence of adult-onset T1D, also called latent autoimmune diabetes in adults (LADA), is controversial. Some in the diabetes community regard LADA and T1D as encompassing a single group of autoimmune diabetes. Others see strong overlaps in genetic, pathophysiologic, and clinical characteristics between LADA and both T1D and T2D, leading to yet another name: type 1.5 diabetes.

Although the American Diabetes Association (ADA) does not currently recognize LADA as a distinct diabetes subtype separate from T1D, it has been discussed in the global diabetes literature for more than a decade—including having proposed diagnostic criteria from the Immunology of Diabetes Society (Table 2). Where the term is used, LADA describes a heterogeneous patient population, making a standard treatment algorithm difficult to define. Other diabetes medications, alone or in combination with insulin, have also been used in patients with LADA to preserve beta-cell function and maintain glycemic control. Treatment should be individualized to match the needs of each patient.

**CASE SCENARIOS**

To help understand the various ways atypical diabetes may present and be misdiagnosed in adults, as well as individualized strategies that may be applied to manage atypical diabetes, consider the following case scenarios.

**CASE 1**

**ROBERT**

Robert is a 50-year-old white man with a BMI of 22 kg/m$^2$ who presented with increased thirst, increased urination, hunger, blurred vision, fatigue, and an unintentional 8-lb weight loss. His hemoglobin A1c (HbA1c) was 9.0%. He had no family history of diabetes. Robert started on 10 units daily of long-acting insulin and metformin while autoantibody testing was completed. When results were strongly positive for anti-glutamic acid decarboxylase (GAD) autoantibodies (98 IU/mL), his metformin was stopped. His long-acting insulin dose was increased to 20 units/day based on fasting glucose values, but, after 2 weeks, he began to develop episodes of hypoglycemia, so his dose was reduced. He was started on continuous glucose monitoring (CGM).

After 4 months, his HbA1c was 6.5%. He was taking 8 units of basal insulin daily, and his CGM device showed an average time-in-range of 95%. He restricted his carbohydrate intake but returned to his normal weight, regaining almost 8 lbs. Robert was referred to a registered dietitian to be sure he was eating properly and was not restricting his carbohydrate intake too much. Over the next year, Robert’s post-breakfast and post-dinner glucose levels routinely increased to more than 160 mg/dL, especially when he ate more than 25 g of carbohydrate per meal. He was started on a pre-meal rapid-acting insulin at a dose of 1 unit per 25 g of carbohydrate with a correction factor of 1:75.

**Case Insight**

- Robert presented with the classic signs and symptoms of T1D, even though he was 50 years old
- Although he was initially given metformin, he was also started on insulin
- Because he was lean, had no family history of diabetes, and had symptoms at diagnosis, the clinical suspicion for adult-onset T1D was very high
- Because he was motivated to maintain good glycemic control without an intensive insulin regimen, it was important to be sure he was achieving adequate nutritional intake
**CASE 2 ANGELA**

Angela is a 30-year-old Hispanic woman with a BMI of 28 kg/m². She presented with central obesity, borderline hypertension, and a positive family history of diabetes, having both a mother and brother with T2D. She also presented with symptoms of frequent vaginal yeast infections and increased urination. She said that she had measured a random blood glucose (BG) of 275 mg/dL using her mother’s glucose meter. Her HbA1c was 10.0%. Laboratory results showed triglycerides of 216 mg/dL and a high-density lipoprotein cholesterol of 37 mg/dL.

Angela was diagnosed with T2D and was started on metformin and a sulfonylurea. After 6 months, her HbA1c was 9.0%. A glucagon-like peptide-1 (GLP-1) receptor antagonist was added to her treatment regimen, but, after 3 months, her HbA1c had reduced only to 8.5%. Basal insulin was then added and titrated to decrease her fasting BG levels. Once her fasting BG was roughly 120 mg/dL, she was placed on a blinded CGM device. CMG results showed a high degree of glycemic variability, especially after eating. Her BG levels were low at night despite taking only 26 units of basal insulin.

Her care team ordered autoantibody testing, which was positive for anti-GAD (18 IU/mL) and ZnT8 autoantibodies (35 U/mL). Angela was diagnosed with T1D. Her T2D medications were stopped, and she started an intensive insulin therapy regimen.

**Case Insight**

- Angela presented like an adult with T2D, but she actually had T1D
- She was misdiagnosed and initially treated with noninsulin medications that did not have an adequate effect on her HbA1c
- The combination of her age and lack of response to noninsulin therapies led her healthcare provider to measure antibodies and correctly characterize her as having T1D

**CASE 3 JACKSON**

Jackson is a 40-year-old African American man with a BMI of 23 kg/m² and a history of T1D. After presenting to an emergency department 5 years ago with mild diabetic ketoacidosis (DKA) and pneumonia, he was admitted, told he had T1D, and started on insulin. He had a strong family history of diabetes (both insulin and non-insulin requiring); his father, uncle, and grandmother had the condition. He had been on a multiple daily insulin regimen since diagnosis, although he occasionally forgot to take his insulin for a week or so while traveling and didn’t notice any changes in how he felt.

At a recent office visit, Jackson’s laboratory results showed a fasting BG of 123 mg/dL and a C-peptide level of 2.8 ng/dL. Testing was negative for anti-GAD and ZnT8 autoantibodies. Metformin and a dipeptidyl peptidase 4 inhibitor (DPP-4) inhibitor were sequentially added to his insulin regimen. His pre-meal insulin doses were reduced as he responded to the oral medications. Eventually, he was weaned off his insulin and maintained on metformin plus a DPP-4 inhibitor.

**Case Insight**

- Jackson presented like a person with adult-onset T1D, but he actually had T2D; his misdiagnosis meant that appropriate treatment with oral medications was delayed for 5 years
- Individuals with T2D, particularly those who are African American, can have DKA at diagnosis and during periods of illness
- The fact that Jackson was relatively lean and young and presented with DKA made the diagnosis of adult-onset T1D more likely, but this should have been confirmed with antibody testing and clinical follow-up to determine which type of diabetes he actually had, particularly because of his strong family history
OTHER TYPES OF ATYPICAL DIABETES

Maturity-Onset Diabetes of Young
Maturity-onset diabetes of young (MODY) is a classic example of monogenic diabetes, in which an abnormality in a single gene leads to beta-cell and insulin secretion dysfunction. MODY is highly heterogeneous, with 14 known subtypes (MODY 1-14) that affect different pathways and result in different clinical presentations, diagnostic criteria, and management approaches. Together, the subtypes of MODY account for 1% to 5% of diabetes cases worldwide. The most common subtypes are MODY-2 and MODY-3; MODY-2 accounts for 32% of MODY cases and is caused by a mutation in the glucokinase gene, whereas MODY-3 accounts for 50% of MODY cases and HNF1α is the affected gene.

Patients with MODY may present as normal-weight children or young adults with mild hyperglycemia and no signs of insulin resistance, leading to clinical suspicion of T1D. Important distinguishing factors for MODY include the absence of diabetes antibodies and a strong family history following an autosomal dominant pattern (ie, diabetes affecting more than 2 generations). A diagnosis of MODY is confirmed by genetic testing of high-risk individuals (based on clinical presentation and family history). Treatment for MODY depends on the affected gene and ranges from diet and lifestyle alone (MODY-2) to sulfonylureas (MODY-3) and other diabetes medications.

Cystic Fibrosis–Related Diabetes
Cystic fibrosis (CF) is an autosomal recessive disease that affects 1 in 2,500 live births. It is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene. The mutation adversely affects the function of the membrane-bound CFTR protein, leading to an imbalance of water movement across epithelial cells and dehydrated cell surfaces. The classic build-up of thick mucus that occurs in the lungs of patients with CF can also occur in the pancreas and other tissues. Approximately 50% of adults with CF who are older than 30 years will develop cystic fibrosis–related diabetes (CFRD), which increases the mortality rate by 6-fold relative to CF alone. As the life expectancy of patients with CF increases, the prevalence of CFRD is also increasing. CFRD is a distinct subtype of diabetes, though it shares features with T1D and T2D. Patients tend to be lean, insulin-deficient adolescents or young adults at the time of diagnosis, consistent with T1D, but CFRD is not an autoimmune condition. In addition, some patients with CFRD experience modest insulin resistance, as seen in T2D. Insulin therapy is the most common approach to CFRD management.

Post-Pancreatectomy Diabetes
Another subtype, sometimes called type 3c diabetes, arises from diseases or injuries to the pancreas leading to deficient insulin production. For more than 75% of these patients, the underlying cause is chronic pancreatitis; other causes include pancreatic cancer and pancreatic surgery. Type 3c diabetes accounts for 4% to 5% of all diabetes cases and is often initially misdiagnosed as T2D (or, less commonly, T1D). Relative to patients with T2D, patients with underlying pancreatic conditions have worse glycemic control and a greater need for insulin.

PATIENT EDUCATION RESOURCES
We hope that you found this to be a helpful overview of adult-onset T1D and other forms of atypical diabetes. The following JDRF resources provide patient education on this topic:
- For adults newly diagnosed with T1D: www.jdrf.org/t1d-resources/newly-diagnosed/
- T1D Care Kit for adults recently diagnosed with T1D: www.jdrf.org/t1d-resources/newly-diagnosed/adults/care-kit/

REFERENCES