# Uncommon Presentations of Diabetes: Zebras in the Herd

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The majority of patients with diabetes are diagnosed as having either type 1 or type 2 diabetes. However, when encountered in clinical practice, some patients may not match the classic diagnostic criteria or expected clinical presentation for either type of the disease. Latent autoimmune, ketosis-prone, and monogenic diabetes are nonclassical forms of diabetes that are often misdiagnosed as either type 1 or type 2 diabetes. Recognizing the distinguishing clinical characteristics and understanding the diagnostic criteria for each will lead to appropriate treatment, facilitate personalized medicine, and improve patient outcomes.

"When you hear hoofbeats, think horses, not zebras." In giving this advice to his University of Maryland medical students in the 1940s, Dr. Theodore E. Woodward meant that most illnesses will have common, not rare, causes. This observation remains relevant today and pertains particularly to those with a diagnosis of diabetes.

Of the estimated 30.3 million Americans with diabetes, 90–95% are diagnosed with type 2 diabetes, and the remaining 5–10% are diagnosed with type 1 diabetes (1). Both are polygenic disorders, involving multiple genes that influence β-cell mass and the regulating functions of insulin secretion and insulin action (2). Type 2 diabetes is associated with relative insulin deficiency, insulin resistance, strong hereditary predisposition, lack of diabetes-associated autoimmunity, obesity, and other metabolic markers (3). Type 1 diabetes is associated with autoimmune destruction of the β-cells, requires lifelong insulin replacement, and has a high risk for diabetic ketoacidosis (DKA) (3). Unlike type 2 diabetes, type 1 diabetes does not have as strong a hereditary component and is not typically associated with obesity as an underlying contributing factor (3). In addition, there are patients whose clinical course does not fully align with the classic diagnostic criteria or expected clinical presentation for either type 1 or type 2 diabetes.

In this article, we review the distinguishing characteristics, diagnostic criteria, and recommended treatments for three types of diabetes that are often misdiagnosed: latent autoimmune diabetes in adults (LADA), ketosis-prone diabetes (KPD), and monogenic diabetes (maturity-onset diabetes of the young [MODY] and neonatal diabetes). These are the zebras that may be found among the herd of horses.

## Latent Autoimmune Diabetes in Adults

### *Background and Basic Definition*

The term LADA is meant to describe autoimmune (type 1) diabetes that occurs during adulthood. The term was first coined in 1994, although 20 years earlier, there was recognition that some adults treated with sulfonylureas had islet cell antibodies and a more rapid progression to insulin deficiency than expected (4). Others have referred to this as type 1.5 diabetes because people with LADA often have some features of both type 1 and type 2 diabetes (5).

In its *Standards of Medical Care in Diabetes—2019* (3), the American Diabetes Association does not identify LADA as a specific type of diabetes but hints that type 1 diabetes may be different in adults in two ways. First, "the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in

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others (mainly adults). Second, "adults may retain sufficient β-cell function to prevent DKA for many years; such individuals eventually become dependent on insulin for survival and are at risk for DKA."

Although there is not a widely accepted definition of LADA or agreement that it is a specific subtype of diabetes, most studies use the following criteria to classify a subject with LADA: *1*) diagnosis of diabetes at >30 years of age, *2*) no requirement for insulin therapy for ≥6 months, and *3*) presence of diabetes-associated autoantibodies (4,6,7). Because of the age of onset, many people with LADA are mistakenly diagnosed with type 2 diabetes, and a correct diagnosis may not be made for years. Laugesen et al. (5) reviewed eight studies on LADA and found that 4–14% of people diagnosed with type 2 diabetes had diabetes-associated autoantibodies. When divided into age-groups, the highest percentage of these individuals was found among those 34–44 years of age (14%), and the lowest was among those 55–64 years of age (7%). Although it is estimated that LADA is the most prevalent form of autoimmune diabetes—more common that childhood-onset type 1 diabetes (3,5)—it often may be initially misdiagnosed as type 2 diabetes, which could lead to inappropriate or delayed treatment (5,6).

## *Pathophysiology*

GAD 65 autoantibodies (GADA) are the most common autoantibody seen in people with LADA and are considered the most specific and sensitive biomarker for LADA (8). Insulin autoantibodies (IAA) are typically found early in the course of diabetes but decrease with increasing age (4). Therefore, by the time an adult is correctly diagnosed with type 1 diabetes or LADA, IAA may not be detected. Insulinoma-associated antigen 2 autoantibodies (IA-2A) are often present in children with type 1 diabetes along with GADA or other autoantibodies, but they do not persist as long as GADA (9). Presence of IA-2A may indicate the presence of susceptible HLA haplotypes and other types of autoimmunity (4). Zinc transporter 8 autoantibodies (ZnT8A) are another type of diabetes-associated autoantibodies that tend to disappear after diagnosis (5). This flux in autoantibodies is not fully understood and points to the lack of homogeneity of all cases of type 1 diabetes.

In the Collaborative Atorvastatin Diabetes Study (CARDS), among adults who were GADA-positive and classified as having LADA, only 0.7% were also IA-2A–positive, and only 0.2% were also ZnT8A-positive (10). All of the adults who were IA-2A– or ZnT8A-positive were also GADA-positive. However, it should be noted that individuals in CARDS had a mean duration of diabetes of 7.9 years, so it would be likely that any diabetes-associated antibodies other than GADA would have waned by that point.

Lack of homogeneity among people with LADA is evident when comparing those with high-titer GADA (GADA-high) and those with low-titer GADA (GADA-low). Those with GADA-high tend to be leaner and younger at diagnosis, have a lower prevalence of metabolic syndrome, exhibit a more rapid decline in C-peptide level and progression to insulin therapy, and have multiple diabetes-associated autoantibodies. In other words, LADA with GADA-high tends to resemble classic type 1 diabetes (4,5).

People with GADA-low LADA tend to be more phenotypically similar to those with type 2 diabetes; they have an increased prevalence of metabolic syndrome and slower decline in β-cell function and progression to insulin therapy (4,5). In the LADA China Study (11), residual β-cell function was detectable in 97% of individuals with type 2 diabetes, 90% of those with GADA-low, and 42% of those with GADA-high after 3 years. The level that differentiates GADA-high from GADA-low is not standardized. CARDS classified GADA-low as 40–200 IU, whereas the LADA China Study used 18–180 IU (10,11).

A study by Castelblanco et al. (12) of obesity-induced inflammatory mediators provided further support for the notion that LADA appears to be an admixture of classic type 1 and type 2 diabetes. The median levels of soluble tumor necrosis factor-α receptor 2 (sTNFRII), a marker of obesity-associated chronic inflammatory state, gradually increased from individuals with type 1 diabetes to those with LADA and from those with LADA to those with type 2 diabetes. The level of sTNFRII was positively correlated with other markers of adiposity, including elevated BMI, greater waist-to-hip ratio, and higher triglyceride levels. Levels of adiponectin, which is produced by adipose tissue and is involved in glucose metabolism, followed the opposite pattern, gradually increasing from those with type 2 diabetes to those with LADA to those with type 1 diabetes (12).

The first genome-wide association study of LADA recently compared 2,634 case subjects of European ancestry with LADA with control subjects with type 1 or type 2 diabetes. This study revealed that, although most signals in the HLA haplotype region in people with LADA were shared with those with type 1 diabetes, there were

novel independent signals at the *PFKFB3* locus in those with LADA (13). LADA has also been shown to share a strong genetic linkage with type 2 diabetes in the transcription factor 7–like gene (6). Additional studies are needed to understand whether LADA is a subtype of type 1 diabetes in adults or a distinct form of diabetes that falls on the spectrum between type 1 and type 2 diabetes.

## Clinical Considerations

Several studies have demonstrated that patients with LADA have higher A1C levels than those with either type 1 or type 2 diabetes. Hernandez et al. (7) reported an average A1C of 7.5% for those with type 1 diabetes, 6.9% for those with type 2 diabetes, and 8.3% for those with LADA. The LADA China Study (11) reported that 53% of patients with type 2 diabetes and 68% of patients with LADA had an A1C >6.9%. In CARDS (10), the average A1C was 7.8% in GADA-negative patients, 8.2% in GADA-low LADA patients, and 8.6% in GADA-high LADA patients. A study in Sweden (14) found that 53% of type 2 diabetes patients and 67.8% of LADA patients had an A1C >7.0%, even though the LADA patients had been on insulin for a longer duration (53.3 vs. 28.8 months). The reasons for these results are unknown, but it has been speculated that they are due to misdiagnosis of LADA as type 2 diabetes, delay in insulin initiation and intensification, and lack of evidence for use of other diabetes medication classes to treat LADA (6,12).

It is well known that people with type 1 diabetes experience a higher frequency of other autoimmune conditions such as autoimmune thyroid disease, which occurs in 17–30%, and celiac disease, which occurs in 1.6–16.4% (3). People with LADA also have a higher frequency of autoimmune thyroid disease, estimated to occur in 27% of GADA-positive patients, with a higher incidence among those with GADA-high versus those with GADA-low (5,6). Therefore, a correct diagnosis of LADA should prompt screening for other autoimmune conditions.

## Treatment

The optimal treatment for LADA is not clear because few studies have been done. Sulfonylureas are not recommended because two randomized controlled studies in Japan found that participants on insulin had better outcomes than those on sulfonylureas (improved C-peptide response and lower A1C in one study and lower progression to an insulin-dependent state in the second study) (5,6). Early insulin therapy is recommended, but studies have shown that even patients with LADA who are on insulin have higher A1C levels than those with other types of diabetes (4,7,11,14), although the type and intensity of insulin therapy has not been reported. One small prospective study found that a dipeptidyl peptidase 4 (DPP-4) inhibitor with insulin glargine was associated with a slower decline in C-peptide levels over 1 year, and two other studies showed improvement in β-cell function with DPP-4 inhibitors in those who have LADA or are GADA-positive (6). Treatment for LADA, particularly in individuals with GADA-low or metabolic syndrome, will also need to include measures to reduce the risk of macrovascular disease (5).

The general consensus in all studies of LADA is that further study is needed. The lack of standardization of LADA diagnostic criteria or even recognition that it is distinct from classic type 1 diabetes limits the interpretation of study results. The variations seen within people with LADA (e.g., GADA-high vs. GADA-low or presence or absence of metabolic syndrome) point to the need for further study to provide evidence-based treatment guidelines and improve outcomes for people with LADA.

## LADA Case Study

S.R. is a 44-year-old white woman who has had type 2 diabetes for 4 years and is referred to a certified diabetes educator for diabetes education and fine-tuning of her insulin regimen. Her medical history includes treatment for hypothyroidism for 6 years. There is no family history of diabetes or thyroid disease. Her father died at the age of 72 years from congestive heart failure; her mother is alive at the age of 74 years and takes blood pressure medications.

S.R.'s current medications include levothyroxine 100 μg daily, metformin 1,000 mg twice daily, and insulin detemir 15 units at bedtime. Her insulin was initiated 2 years ago at 10 units. Her pertinent laboratory results include A1C 8.9%, fasting blood glucose 68 mg/dL, and lipids and vitamin D levels within normal parameters. She has a BMI of 23 kg/m$^2$, walks for 45–60 minutes most days, and eats a generally healthful diet. She complains of frequent fasting and pre-dinner hypoglycemia, especially after walking.

The diabetes educator asks S.R. to begin checking her blood glucose more frequently, including before and 2 hours after meals. She also orders professional continuous glucose monitoring (CGM).

S.R.'s blood glucose testing and CGM data confirm her reports of hypoglycemia but also reveal postprandial hyperglycemia (200–400 mg/dL). The diabetes educator recommends adding mealtime insulin and lowering her dosage of basal insulin. Laboratory testing is performed to confirm the suspicion of LADA; she is found to have a low C-peptide level (0.3 mg/dL), to be positive for GADA (120 IU/mL), and to be negative for IAA.

Although S.R. was initially resistant to adding mealtime insulin, receiving the correct diagnosis helped her accept the need for multiple daily injections and led to improvement in her A1C and fewer glycemic excursions. With the correct diagnosis, she will be more likely to get insurance approval for insulin pump therapy and use of a personal CGM device should she decide to pursue those. Her provider decided to discontinue metformin in this thin, insulin-deficient, insulin-sensitive patient, and she was given education on DKA risk, prevention, and treatment because of her low C-peptide level.

Therapeutic inertia was evident in this case. S.R. had an A1C of 8.9%, but her insulin regimen had been minimally intensified from 10 to 15 units of basal insulin over 2 years.

## Ketosis-Prone Diabetes

### *Background and Basic Definition*

DKA is an acute, life-threatening complication resulting from hyperglycemia and absolute insulin deficiency. It is most typically associated with patients with type 1 diabetes at initial diagnosis or secondary to inadequate insulin therapy. It is also known to occur in patients with either type 1 or type 2 diabetes when there are precipitating (provoking) factors that pose significant metabolic stress (e.g., severe burns, sepsis, myocardial infarction, and pancreatitis) (15). However, DKA can also be unprovoked, occurring with no identified precipitant. Most people with KPD will present with unprovoked DKA. This type of diabetes has also been referred to as idiopathic type 1 diabetes (3), atypical diabetes (16), Flatbush diabetes (17), and type 1B diabetes (18).

### *Clinical Considerations*

The true prevalence and incidence of KPD remains unknown, but it is more likely to occur in people of African, Caribbean, Asian, or Hispanic descent (19–22). Other common clinical characteristics include male sex (3:1 ratio), overweight or obesity, <30 years of age, strong family history of diabetes, lack of autoantibodies typically associated with type 1 diabetes, and positive signs of insulin resistance (e.g., acanthosis nigricans) (19,22,23).

KPD is of clinical significance because it is the underlying cause of 25–60% of hospitalizations for new-onset DKA in Hispanics and African Americans (24). Once KPD has been diagnosed, it is then important to properly classify the subtype to determine prognosis and future treatment.

### *Pathophysiology*

The underlying cause and specific genetic basis for KPD remain unknown, and no specific test or group of tests are currently available to aid in diagnosis. However, several factors have been identified that relate to both predisposition to KPD and eventual insulin dependence. For example, potential predisposing factors in people of West African descent may include an alteration of the *PAX4* gene (25) and the coexistence of glucose-6-phosphate dehydrogenase deficiency (26). Factors potentially associated with a higher possibility of discontinuing insulin therapy include lower leptin and higher adiponectin levels (27) and the absence of autoimmune markers (28).

There are four subtypes of KPD, and the correct categorization will guide prognosis and treatment. The "Aβ" classification scheme (29) is highly accurate for determining the subtype and predicting the need for insulin (30). This scheme has two components: the presence or absence of antibodies [A + or –], specifically for GADA, IA-2A, and ZnT8A (29,31) and the indication of intact β-cell function [β + or –] (29). β-Cell function is assessed by evaluating C-peptide levels. However, severe hyperglycemia causes glucotoxicity of the pancreatic β-cell, and C-peptide levels obtained during the acute stage may be inaccurately low. Therefore, testing should be performed several weeks after DKA resolves (20,32). Intact β-cell function is defined as a positive C-peptide level >1 ng/mL (fasting) or >1.5 ng/mL (stimulated) (29).

The four subtypes in the Aβ classification scheme are as follows:

1. A–β+ (negative antibody status, positive C-peptide level). This is the most common type of KPD, affecting ~50% of people with KPD, and its course closely mimics the prognosis for type 2 diabetes (29). Roughly 70% of patients with this subtype will not require insulin treatment (33).

2. A–β– (negative antibody status, negative C-peptide level). This subtype affects ~22% of people with KPD, and the associated β-cell injury is caused by either mechanical or unidentified autoimmune processes (29). Most of these patients will require lifelong insulin therapy.
3. A+β– (positive antibody status, negative C-peptide level). This subtype affects ~17% of people with KPD. Its presentation, course, and prognosis are identical to that of autoimmune type 1 diabetes and thus there is debate as to whether this is really a subtype of KPD (29,34). All patients with this subtype will require lifelong insulin therapy, and the risk for recurrent DKA is high (29).
4. A+β+ (positive antibody status, positive C-peptide level). This subtype is diagnosed in ~11% of patients with KPD (29) and shares characteristics with LADA (35). The distinguishing characteristics for KPD are initial presentation in DKA and immediate need for insulin that is not seen with LADA (36). In addition, the A+β+ result could also be found in those with autoimmune diabetes who have experienced remission or a "honeymoon phase" (37,38). Nonetheless, ~50% of patients with this classification will require insulin therapy as β-cell destruction progresses (29). Close monitoring, including C-peptide reevaluation every 6 months, is recommended, especially during the initial 12 months after the index DKA event (20,29).

### *Treatment*

Patients will most often present with the hallmark feature of acute, unprovoked DKA and will require insulin (29). However, unlike patients with type 1 diabetes, most will not require exogenous insulin for glucose management within a few weeks of the index DKA event (33,39). The vast majority will be classified as A–β+. They will have a low risk for recurrent DKA, and their clinical course and treatment will be similar to what would be expected with type 2 diabetes. Therefore, many patients should be able to manage KPD with nutrition modifications, increased physical activity, and weight loss.

The need for pharmacologic interventions with both noninsulin and insulin agents will be determined by ongoing disease progression and development of comorbidities and complications that ultimately determine the efficacy and safety of noninsulin therapies (40). It is important to note that agents belonging to the sodium–glucose cotransporter-2 inhibitor class are associated with an increased risk of DKA in patients with type 2 diabetes and are also not currently approved for use in patients with type 1 diabetes in the United States (41). Whether the same risk for DKA applies to patients with KPD is unknown. Thus, more information is needed before considering these agents.

Patients classified as having no β-cell reserve (β–), regardless of their antibody status, should not have insulin discontinued because the risk for recurrent DKA is high. Those who present with provoked DKA and are able to initially discontinue insulin will typically require it again within 3–4 years of the index DKA event (42). Therefore, these patients must remain closely monitored.

A review of the literature did not reveal a difference in the risk of developing diabetes-related complications among patients with KPD compared to those with either type 1 or type 2 diabetes. Therefore, optimal management of blood glucose, blood pressure, lipids, and weight, along with proper screening for complications, is recommended (43–46).

### *KPD Case Study*

D.T. is a 32-year-old African-American man who was referred with a diagnosis of type 1 diabetes 18 months ago. He presented to the emergency department with a serum glucose >800 mg/dL and DKA. He was symptomatic with polyuria and polydipsia for 3 weeks but denied any illness, trauma, or alcohol or illicit drug use at the time of presentation. He is 5 feet, 8 inches tall, weighs 154 lb, and has a BMI of 23.5 kg/m$^2$. At diagnosis, he weighed 210 lb and had a BMI of 31.9 kg/m$^2$, but he has since lost weight with improved nutrition and increased physical activity.

He was initially prescribed insulin, but his dose was reduced by at least 50% ~1 month later due to hypoglycemia, and over the past year, he has required "hardly any" insulin. He denies recurrent DKA and maintains his weight by eating healthier and performing military-required physical exercises. D.T. believes he does not have type 1 diabetes and wants his medical record corrected because this diagnosis is placing him at risk for discharge from the military.

He currently takes no medications other than the prescribed insulin. His medical history includes hypertension (resolved with weight loss). He denies having been diagnosed with dyslipidemia, cardiovascular disease, or autoimmune disorders. His family history is significant for type 2 diabetes and obesity in both parents and two of three siblings. His mother is alive at the age of 63 years and has coronary heart disease and

hypertension. His father died at the age of 70 years from a myocardial infarction. His third sibling is healthy, and there is no family history of autoimmune disorders.

D.T.'s current pertinent laboratory results include A1C 6.1%, fasting glucose 118 mg/dL, fasting C-peptide 2.7 ng/mL, GADA-negative, IA-2A–negative, and ZnT8A-negative. His physical exam is significant only for acanthosis nigricans on his neck.

D.T. does not have type 1 diabetes; his correct diagnosis is that of unprovoked KPD, subtype A–β+. This diagnosis is supported by the above laboratory findings, his initial history of hyperglycemia with unprovoked DKA, and his clinical course, which involved the eventual discontinuation of insulin without recurrent DKA.

It is important to emphasize the lifestyle modifications D.T. has integrated into his routine. Proper nutrition, physical activity, and maintaining an appropriate weight have put his diabetes into remission and are essential components of lifelong diabetes management.

Because his disease course is expected to mimic that typically seen in patients with type 2 diabetes, his counseling must include that eventually he may require pharmacologic therapy, which could include insulin. The signs and symptoms of DKA should be discussed with clear instructions provided regarding when to seek emergent care. Referral to a certified diabetes educator is indicated for additional diabetes education and support (43). His blood pressure and lipids must be monitored and treated to meet current recommendations (46). Whereas D.T. has managed to maintain significant weight loss, many patients with KPD will be overweight or obese at presentation. These conditions will affect control of glucose, blood pressure, and cholesterol and must be addressed (45).

## Monogenic Diabetes

Monogenic forms of diabetes are caused by single gene mutations or abnormalities that, on their own, are sufficient to cause diabetes. In contrast, polygenic conditions such as type 1 and type 2 diabetes result from the interactions of multiple genetic risk factors and environmental factors. Within the umbrella term of monogenic diabetes, four main subgroups exist: neonatal or congenital diabetes, MODY, syndromic forms, and mitochondrial diabetes. Although heterogenous, most of the genes that cause monogenic diabetes are important for β-cell function or pancreatic development.

These conditions may affect 1–5% of all people with diabetes; however, as many as 80% may be undiagnosed or misdiagnosed (47–55). Although monogenic diabetes is relatively rare, the clinical impact of correctly diagnosing these conditions is significant in terms of tailoring treatment to the genetic mutation, guiding monitoring for co-occurring conditions, and providing information for family planning. Although suspicion for monogenic diabetes can be raised through clinical features, genetic testing is required for diagnosis. Such testing can be cost-effective in appropriately selected adults (56) and cost-saving for neonatal diabetes and monogenic diabetes in pediatric patients (57,58). Correctly diagnosing and treating patients with monogenic diabetes is an excellent example of personalized medicine in diabetes.

### *Neonatal or Congenital Diabetes*

Neonatal diabetes is a term generally used to describe monogenic forms of diabetes diagnosed at <1 year of age. Because many of these cases are diagnosed outside of the true neonatal period (up to 1 month of age), congenital diabetes or infancy-onset diabetes may be a more appropriate term.

The majority of cases diagnosed with diabetes between birth and 6 months of age will have a monogenic cause, whereas the likelihood of a monogenic cause decreases to only 5–10% in those diagnosed between 6 and 12 months of age (52). Early-onset autoimmune type 1 diabetes makes up the remaining 90–95% of these cases.

Although diabetes autoantibody testing can be useful to help distinguish congenital diabetes from early-onset type 1 diabetes, genetic testing is the only way to make a clear diagnosis. Congenital forms of diabetes may be permanent or transient. Transient cases often occur within the first few weeks of life, with a normalization of blood glucose levels after a few months, and often have a reoccurrence of diabetes around puberty. Some forms of congenital diabetes cause diabetes in isolation, whereas others cause additional medical conditions such as learning difficulties, congenital heart defects, or pancreatic exocrine insufficiency.

#### Prevalence

The prevalence of congenital diabetes varies by country, rates of consanguinity, and definition of congenital diabetes used, but an overall estimate is ~1 in every 100,000 births (50–54).

## Clinical Features

Clinical characteristics of congenital diabetes often include:

- Diagnosis of diabetes at <1 year of age
- Could be permanent or transient
- Negative for diabetes-related autoantibodies
- DKA at diagnosis is frequent in infancy-onset diabetes, but may or may not be present depending on the gene affected and diagnosis age (59)
- May not have an affected parent (more likely than MODY to be de novo, or spontaneously inherited)
- May have other associated features, such as congenital heart defects, pancreatic exocrine insufficiency, or developmental delays

## Most Common Forms of Congenital Diabetes

### KCNJ11/ABCC8 *Mutation*

About 50% of permanent congenital diabetes cases are caused by mutations in either the *KCNJ11* or *ABCC8* gene (52,60). Such mutations affect the function of ATP-dependent potassium channels in β-cells, ultimately inhibiting insulin release. They can also cause transient congenital diabetes. Nearly all cases can be managed with oral sulfonylureas instead of insulin, often resulting in improved blood glucose levels (61). Sulfonylurea trials can be completed using existing protocols (61) or in consultation with expert centers (e.g., The University of Chicago [monogenicdiabetes.org] or the University of Exeter [diabetesgenes.org]). These mutations affect ATP-dependent potassium channels in both the pancreas and the brain, and thus some mutations cause a range of neurodevelopmental challenges such as learning and behavioral difficulties (62–67). Initiating sulfonylurea therapy at a young age may improve both diabetes and developmental outcomes (68–70). Although high doses are often required, sulfonylurea therapy appears to be both safe and durable in this population (71,72).

#### *Insulin Gene Mutation*

Mutations in the insulin gene (*INS*) are the second most common cause of permanent congenital diabetes and typically cause diabetes in isolation (60,73). These mutations inhibit proper proinsulin processing, resulting in misfolded proteins that likely lead to β-cell stress and death (74). Most patients with *INS*-related diabetes will require lifelong insulin treatment. Intensive insulin therapy at the first sign of diabetes may help to preserve β-cell function and improve outcomes in these cases, further highlighting the need for early genetic testing (75).

#### *6q24 Abnormalities*

Methylation abnormalities at the chromosome 6q24 locus, causing over-expression of imprinted genes in that region, are the most common cause of transient congenital diabetes (76,77). Hyperglycemia typically begins within the first few weeks of life, remits around the age of 1 year, and reoccurs around puberty. Other features often include intrauterine growth restriction, umbilical hernia, and macroglossia (78). Although insulin is typically used for treatment, noninsulin therapies may be effective during both the initial infancy period and when diabetes returns later in life (79–81).

### GATA6/GATA4 *Mutations*

Although less common, mutations in the *GATA6* or *GATA4* genes are important because they affect pancreatic development and thus can cause pancreatic hypoplasia or complete agenesis (82–85). Patients with these forms of congenital diabetes also frequently have congenital heart defects and pancreatic exocrine insufficiency.

## Congenital Diabetes Case Study

K.X. is a Hispanic white male infant who initially presented to a local emergency room at 2 months of age. Caregivers noticed he was behaving oddly, seemed weak, and had recently lost 3 lb, although he was drinking more milk than usual. His was found to be overtly hyperglycemic and in DKA. Tests for diabetes-related autoantibodies were negative. Insulin was initiated to stabilize glucose levels. Because of his young age at diagnosis and thus his potential for having *KCNJ11*- or *ABCC8*-related neonatal diabetes, a trial of a sulfonylurea was performed using established protocols while awaiting genetic testing results (61,86,87). He was responsive to the sulfonylurea, and insulin was discontinued.

K.X. was born at 39 weeks' gestation, weighing 2,750 g (small for gestational age). He had no other pertinent medical history and was meeting milestones at the time of his diagnosis. His mother and father did not have any known blood glucose problems. Genetic testing revealed a missense mutation in *KCNJ11* leading to an amino acid substitution from arginine to cysteine at position 201 (c.601C>T, p.Arg201Cys). This mutation was previously reported to be associated with neonatal diabetes (88).

At a follow-up visit when he was 5.5 months old, K.X. was doing well on glyburide 0.58 mg/kg/day. His treatment plan included continuing the glyburide, increasing the dose as needed as he grows; monitoring his development; referring to support services if needed; and performing genetic testing on his family members.

### Summary

We recommend genetic testing for anyone diagnosed with diabetes at <1 year of age. Identification of a congenital form of diabetes may greatly affect the course of treatment and screening for associated conditions and inform the likelihood of recurrence risk for family members.

## *Maturity-Onset Diabetes of the Young*

MODY, the most common subgroup of monogenic diabetes, is characterized by inherited, young-onset diabetes caused by mutations in one of the 14 genes that have thus far been associated with MODY (89). Mutations in these genes can cause a range of phenotypes that usually include diabetes onset during the first 30–35 years of life without typical features of type 1 or type 2 diabetes. MODY is an autosomal-dominant condition; therefore, if a parent has MODY, each of his or her children has a 50% chance of also carrying the MODY mutation. This pattern results in a strong, linear family history of diabetes that is usually diagnosed at <35 years of age and usually without obesity at diagnosis. Additional clinical features and laboratory values can help to distinguish MODY from other forms of diabetes.

### Prevalence

MODY affects ~2% of all people with diabetes (47–49). *HNF1A*-MODY is the most common form in the United Kingdom (90), whereas *GCK*-MODY is the most commonly reported form in other countries, such as the United States, Spain, and Germany (91–93).

### Clinical Features

Features that may increase clinical suspicion of MODY include:

- Diabetes onset occurring before the age of 35 years
- Negative results for diabetes-related autoantibody tests
- Normal BMI at diagnosis
- Evidence of endogenous insulin production >3 years after diagnosis (lower insulin requirements than expected, positive C-peptide)
- No signs of metabolic syndrome such as obesity, acanthosis nigricans, or elevated lipids
- Strong, linear family history of diabetes diagnosed at <35 years of age
- *GCK*-MODY: stable, mild fasting hyperglycemia (~100–140 mg/dL, A1C 5.6–7.6% [94,95]) plus the features above
- *HNF1B*-MODY: renal abnormalities (particularly renal cysts or structural abnormalities) and genitourinary abnormalities, plus the features above
- *HNF1A*-MODY: low renal threshold for glucosuria and sensitivity to sulfonylureas
- *HNF4A*-MODY: macrosomia and hypoglycemia in infancy and sensitivity to sulfonylureas

### Most Common Forms of MODY

#### GCK-*MODY (Previously Called MODY2)*

*GCK* encodes for glucokinase, an enzyme that acts as the body's glucose sensor. This enzyme senses when glucose levels are elevated and, in turn, modulates insulin release (96). People with *GCK*-MODY have a slightly elevated set point for insulin release, which results in mildly elevated fasting plasma glucose (FPG) (~100–140 mg/dL) with A1C levels of ~5.6–7.6% (94,95). This mild fasting hyperglycemia is lifelong and quite stable over time with a mild increase in older age, as also occurs in people without any form of diabetes (97).

*GCK*-MODY is estimated to affect 1 of every 1,000 people (98), including many who are not aware of their mildly elevated blood glucose. Many individuals with *GCK*-MODY are found to have hyperglycemia incidentally, such as through routine physicals or insurance screenings, or during a woman's first pregnancy.

Managing *GCK*-MODY with glucose-lowering medications is not recommended outside of pregnancy because treatment does not affect the genetically elevated set point or change A1C (99). In addition, these mildly elevated glucose levels have not been associated with a high prevalence of diabetes-related complications compared to unaffected individuals (100). Although patients with *GCK*-MODY were found to have a higher frequency of retinopathy (30%) compared to control subjects (14%), this occurrence mainly comprised background retinopathy, and no cases required laser therapy (100). Women with *GCK*-MODY who are pregnant may require medication depending on the fetus' genotype (101–104).

*GCK*-MODY is not known to be protective against type 1 or type 2 diabetes; therefore, A1C values that increase above a person's typical range should lead to a reevaluation for other more common forms of diabetes.

### HNF1A-*MODY (Previously Called MODY3) and* HNF4A-*MODY (Previously Called MODY1)*

*HNF1A* and *HNF4A* encode for transcription factors that regulate the expression of multiple genes in the liver and pancreas (105–107). In these forms of MODY, antibody-negative diabetes typically presents in adolescence or early adulthood without features suggestive of type 2 diabetes.

Many of these patients, particularly those with *HNF1A*-MODY, exhibit a pronounced sensitivity to sulfonylureas and maintain target blood glucose levels on oral medications alone (108–111). Individuals with *HNF1A*-MODY often exhibit glycosuria at relatively low glucose levels (112) (i.e., <200 mg/dL) and may have elevated HDL cholesterol compared to those with type 2 diabetes (113). Individuals with *HNF4A*-MODY may have been born large for gestational age and may have had transient hyperinsulinemic hypoglycemia during infancy.

These features, as well as plasma glucose and patients' highest A1C value, can be useful in discriminating *HNF1A*- and *HNF4A*-MODY from *GCK*-MODY. Many patients with *HNF1A*- or *HNF4A*-MODY will have an A1C level higher than the *GCK*-MODY range (>7.6%). Patients with *HNF1A*- or *HNF4A*-MODY may have a normal FPG during the early stages of these progressive conditions, whereas patients with *GCK*-MODY will have FPG values in the *GCK*-MODY range (~100–140 mg/dL) (114). The glucose increment in an oral glucose tolerance test can also be helpful. Those with *GCK*-MODY typically have a very small 2-hour glucose increment (often <54 mg/dL), whereas those with *HNF1A*- or *HNF4A*-MODY may have an increment >90 mg/dL (114).

### HNF1B-*MODY (Previously Called MODY5)*

*HNF1B* encodes for a transcription factor that is important for proper development of the kidneys and pancreas (115). Abnormalities in this gene, which are often deletions, can cause diabetes in isolation, renal disease (typically renal cysts) in isolation, or both. Therefore, a linear family history of either or both conditions is typically present. Mutations in *HNF1B* can additionally present with numerous other medical problems such as genitourinary defects or elevated liver enzymes (116,117). Although some patients may respond to noninsulin medications initially, they typically experience progressive β-cell decline, and thus insulin therapy is often required (118).

### *MODY Case Study*

B.L. is a non-Hispanic white woman who was incidentally found to have high blood glucose at the age of 21 years. Laboratory work at a routine physical examination revealed a fasting blood glucose of 120 mg/dL without symptoms of hyperglycemia. She did not have any other medical problems. She returned 2 weeks later for repeat testing. Her fasting glucose at that time was 116 mg/dL, and her A1C was 6.2%. Her BMI was 28.3 kg/m$^2$. She was diagnosed with prediabetes, instructed to lose weight and exercise, and asked to return in 6 months.

At the 6-month follow-up visit, her BMI had decreased to 23.5 kg/m$^2$. Her fasting glucose was 127 mg/dL, and her A1C was 6.4%. She was diagnosed with diabetes, started on metformin, and referred to an endocrinologist. Results of antibody testing were negative (GADA 0.00, islet cell antibody 0.00).

B.L. had a strong, linear family history of "borderline" diabetes. Her father was initially found to have mildly elevated blood glucose in college. When he entered his 50s, he was formally diagnosed as having diabetes and started on metformin. At the time of her visit, he was in his 60s, overweight, and taking metformin and pioglitazone, although they had no appreciable impact on his blood glucose. She had five siblings, three of whom had slightly elevated fasting blood glucose (100–120 mg/dL) and normal BMIs. She had one son who was noted to have slightly high blood glucose after birth without other medical problems.

A clinical suspicion of MODY was raised based on her relatively stable, mildly elevated fasting hyperglycemia, antibody negativity, normal BMI, lack of metabolic syndrome, and strong, linear family history of similar features. Genetic testing revealed a missense mutation in *GCK* leading to an amino acid substitution from methionine to threonine at position 393 (c.1178T>C, p.Met393Thr). This mutation was previously reported to be associated with *GCK*-MODY (119).

The treatment plan included discontinuing all medications and performing genetic testing on family members.

### Summary

Identifying patients with monogenic diabetes is important but can be challenging. Unique clinical features, particularly when they do not fit the typical phenotypes of type 1 or type 2 diabetes, may aid health care professionals in recognizing these families. A correct diagnosis can help guide treatment and improve clinical

**TABLE 1** Comparison of Type 1 Diabetes, Type 2 Diabetes, and Less Common Types of Diabetes

| | Type 1 Diabetes | Type 2 Diabetes | LADA | KPD | Neonatal/ Congenital Diabetes | MODY |
|---|---|---|---|---|---|---|
| Etiology | Polygenic | Polygenic | Polygenic | Polygenic | Monogenic | Monogenic |
| Age at presentation | Any age but usually younger | Any age but usually older | >30 years | Any age, typically male (3:1) | <1 year | Usually <30 years |
| Ethnicity | Any, but more frequent in non-Hispanic white populations | Any, but more frequent in American Indian, Black, Hispanic, and Asian populations | Any | Any, but more frequent in Afro-Caribbean, Hispanic, and Asian populations | Any | Any |
| Diabetes autoantibodies | Present | Absent | Present | Most often absent | Absent | Absent |
| Likelihood of DKA | High | Low | Increasing risk as C-peptide level declines | DKA at onset, most often unprovoked; variable lifelong risk | Depending on gene, moderate to high | Depending on gene, ketosis may be mild or absent |
| Family history | Infrequent | Frequent | Unknown | Frequent, strong | May be infrequent (de novo mutations) or strong and linear (up to 50% of family members affected) | Most forms are dominant inherited with up to 50% of family members affected, but de novo mutations also seen |
| Treatment | Insulin therapy | Lifestyle modification; noninsulin and insulin agents as needed | Early insulin therapy recommended; lack of studies on other agents | Insulin initially; ongoing requirement dependent on subtype; for most, lifestyle modification and noninsulin agents | Should be tailored to gene mutation; may include insulin or sulfonylureas | Should be tailored to gene mutation; may include insulin, oral medications, or no treatment |

Adapted from ref. 120.

outcomes for patients and their family members. Therefore, it is crucial to pursue genetic testing in cases with a high clinical suspicion for monogenic diabetes.

## Conclusion

There are numerous variations of diabetes that present atypically, are associated with underlying genes or causes that are not fully understood, and follow clinical courses that differ from both type 1 and type 2 diabetes. Unfortunately, patients are often misclassified because of characteristics that overlap with those of more common forms of diabetes (Table 1). Distinguishing subtle differences and correctly diagnosing each patient's type of diabetes may be time-consuming and costly. However, this effort is also necessary to properly monitor disease progression, guide safe and appropriate treatment, and identify those at risk for developing acute and chronic complications. Additionally, identifying the correct diagnosis may be emotionally rewarding for patients, especially if the correct diagnosis alters treatment and otherwise positively affects the patient's quality of life.

At times, there are indeed unusual presentations for common diseases. The next time you hear hoofbeats, although you may be wise initially to think horses, look closely. You might be surprised to find a zebra in the herd.

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K.L.S. is an independent contractor/certified product trainer for Medtronic and Tandem. L.M.N. is on the speakers bureaus of AstraZeneca, Janssen, and Novo Nordisk and is a consultant to and advisory board member for Novo Nordisk and Sanofi. No other potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

K.L.S., L.R.L., and L.M.N. all researched data, wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. K.L.S. is the guarantor of this work and, as such, had full access to all the references used and takes responsibility for the integrity and accuracy of the manuscript.

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