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Monogenic Diabetes: the Impact of Making the Right Diagnosis

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Abstract

Purpose of review: Monogenic forms of diabetes have received increased attention and genetic testing is more widely available, however many patients are still misdiagnosed as having type 1 (T1D) or type 2 diabetes. This review will address updates to monogenic diabetes prevalence, identification, treatment, and genetic testing.

Recent findings: The creation of a T1D genetic risk score and the use of non-invasive urinary C-peptide creatinine ratios have provided new tools to aid in the discrimination of possible monogenic diabetes from likely T1D. Early, high dose sulfonylurea treatment in infants with a *KCNJ11* or *ABCC8* mutation continues to be safe and effective. As the field moves towards more comprehensive genetic testing methods, there is an increased opportunity to identify novel genetic causes. Genetic testing results continue to allow for personalized treatment but should provide patient information at an appropriate health literacy level.

Summary: Although there have been clinical and genetic advances in monogenic diabetes, patients are still misdiagnosed. Improved insurance coverage of genetic testing is needed. The majority of data on monogenic diabetes has been collected from Caucasian populations, therefore, research studies should endeavor to include broader ethnic and racial diversity to provide comprehensive information for all populations.

Keywords

monogenic diabetes; MODY; neonatal diabetes; infancy-onset diabetes; congenital diabetes

Introduction

The recognition of heterogeneity within diabetes, beyond type 1 (T1D) and type 2 (T2D), continues to expand. One example of this is monogenic diabetes, which is a broad term that includes Maturity Onset Diabetes of the Young (MODY), congenital, infancy-onset, or ‘neonatal’ diabetes, and syndromic forms. Although diverse in nomenclature, these subtypes are similar in that they are caused by single mutations or abnormalities in genes critical for beta-cell function or glucose regulation. Although monogenic forms of diabetes have been described in the literature since the 1970s (1), many patients continue to go undiagnosed or

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Conflicts of interest

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remain misclassified as T1D or T2D. An accurate diagnosis of monogenic diabetes can provide an opportunity for personalized medicine, including tailoring diabetes treatment plans, guiding the diagnosis and treatment of other associated conditions, and informing testing of family members. This review will cover the prevalence, diagnosis, and management of monogenic diabetes, focusing on updates within the last two years.

Prevalence

Broadly, monogenic diabetes is estimated to affect approximately 2% of people with diabetes. Based on 2015 estimates, this would equal over 600,000 people in the United States alone (2). A recent study of Northern Europeans found a frequency consistent with these estimates by performing targeted sequencing of 225 known or suspected monogenic diabetes genes (3). Of 6888 participants tested, a monogenic form of diabetes was identified in 2.2% of those diagnosed with early onset diabetes (<age 40 years) and only 0.7% with late-onset diabetes, suggesting that age at diagnosis may be a useful clinical parameter in defining likelihood of monogenic diabetes. A separate cohort from the United Kingdom (96% Caucasian) found monogenic diabetes in 2.5% of pediatric (<20 years old) diabetes patients (4). It is important to note that these cohorts were racially homogenous, and thus data from diverse cohorts are needed to confirm the frequency of monogenic diabetes as ~2%.

Congenital Infancy-Onset Diabetes

The infancy-onset subgroup of monogenic diabetes is commonly referred to as neonatal diabetes. However, because diabetes is often diagnosed well beyond the first month of life, we prefer the term congenital diabetes or infancy-onset diabetes, although the latter may include early-onset T1D. The incidence of congenital diabetes is estimated as 1 out of every 100,000 live births, although this can vary widely based on location, primarily dependent on rates of consanguinity (5–7). For example, the incidence of permanent neonatal diabetes in the Al-Madinah region of Saudi Arabia was estimated as just less than 1 out of every 21,000 live births (8). The SEARCH for Diabetes in Youth study estimated the population prevalence of permanent congenital diabetes in United States youth age 20 years or younger to be around 1 in 250,000 (9). These estimates also depend on which diagnosis age cutoff is used, such as less than 6 months or less than 12 months at monogenic diabetes diagnosis, and whether patients with a transient or permanent phenotype are included.

Dominant heterozygous mutations in *KCNJ11* are the most common cause of permanent neonatal diabetes in non-consanguineous families (7,10), followed by mutations in the insulin gene (*INS*) (11,12). Approximately 70% of cases with transient neonatal diabetes will have a methylation abnormality in the 6q24 region (13), while mutations in *ABCC8*, *KCNJ11*, *INS*, or *HNF1B* can also cause transient diabetes (14–16). Recessively-inherited *EIF2AK3*, *INS*, and *GCK* mutations are more common in consanguineous families (7). Some of the more common gene causes include the following:

KCNJ11 and *ABCC8*

KCNJ11 and *ABCC8* encode separate proteins that make up the ATP-dependent K⁺ + channel (KATP channel) in the beta-cell. Activating mutations in either of these

genes cause congenital diabetes with onset within the first year of life (10,17,18). KATP channels are also expressed in the brain, and thus patients with these mutations may also have developmental delay and/or behavior concerns ranging from mild to severe (19–22). These patients are usually responsive to oral sulfonylurea medication, although they can require high doses up to 2.0 mg/kg/day (discussed further in Treatment section below).

INS

Mutations in the insulin gene can lead to abnormal protein folding and, eventually, beta-cell death (23). Clinically, infancy-onset cases with *INS* mutations will require lifelong insulin therapy (15).

Transient diabetes and 6q24 methylation abnormalities

Multiple mechanisms can lead to hypomethylation within the 6q24 differentially methylated region, which together are the most common causes of transient infancy-onset diabetes. Most patients present with severe growth restriction and diabetes onset with the first few days of life. A remission occurs usually within the first year of life, with a diabetes reoccurrence often during adolescence (13), although a case with permanent diabetes has now been described (24).

EIF2AK3

Biallelic mutations in *EIF2AK3* cause Wolcott-Rallison syndrome, which may include infancy-onset diabetes, epiphyseal dysplasia, acute liver failure, developmental delay, and occasionally hypothyroidism and exocrine pancreatic insufficiency (25,26).

MODY

Results from a large cohort in the United States estimated the prevalence of MODY to be at least 1.2% of the pediatric diabetes population (27). Of those who were found to have MODY mutations, 64% identified as a minority ethnicity. The most common forms of MODY are due to mutations in *HNF1A*, *GCK*, and *HNF4A*. The form that is considered the most common may vary by estimation method (population-based screening versus patient-facilitated research study). For example, in a cohort of patients from the United Kingdom, *HNF1A*-MODY was the most common form (52%) (28), whereas in our cohort of patients from the United States, *GCK*-MODY is the most common form (59%, unpublished data). Whether this difference is due to selection bias or true population differences between countries requires further study.

GCK-MODY

GCK encodes for the first rate-limiting enzyme in glycolysis, glucokinase. Glucokinase is often referred to as the ‘glucose sensor’ of the beta-cell. Clinically, persons with these mutations exhibit stable, mild fasting hyperglycemia from birth (~100–140 mg/dl; HbA1c ~5.6–7.8, (29)), although this mild hyperglycemia often goes undiscovered and is picked up only incidentally through a routine physical or during pregnancy. There is no increased complication risk due to these mildly

elevated blood glucose levels (30), and treatment is typically not recommended, as discussed in the Treatment section below. These mutations are estimated to be found in 1 out of every 1,000 people (31).

HNF1A- and HNF4A-MODY

HNF1A and *HNF4A* are critically important transcription factors in liver and pancreas. Patients with these forms of MODY exhibit clinical similarities, although mutations in *HNF1A* are more common. Diabetes diagnosis typically occurs before age 30 years with negative diabetes autoantibodies. A pronounced hypersensitivity to sulfonylureas may exist, particularly for those with HNF1A-MODY. A genotype-phenotype correlation has been described for *HNF1A*, with mutations in exons 1–6 causing a more severe phenotype than those in exons 8–10 (32,33).

Other forms of MODY

There are currently 14 recognized forms of MODY (34). HNF1B-MODY often causes renal or genitourinary abnormalities, such as renal cysts and/or diabetes. Recent studies have found that patients with HNF1B-MODY may have an increased likelihood of intellectual disabilities or learning disabilities (35). Heterozygous *PDX1* mutations can cause MODY, although many benign variants also exist in *PDX1*, highlighting the importance of interpretation of any genetic testing results.

Monogenic forms of autoimmunity

Several additional genes have been described as causes of monogenic forms of autoimmunity over the past few years. These mutations affect critical immune function leading to early onset polyautoimmune disease such as immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome (36–38), although clinical heterogeneity exists in many of these conditions (39). Infancy-onset autoimmune diabetes has been associated with mutations in genes such as *FOXP3*, *IL2RA*, *LRBA*, *STAT1*, and *STAT3*. These patients can test positive for pancreatic autoantibodies (40), but analyzing a T1D genetic risk score may be helpful in discriminating those with a monogenic autoimmune etiology from those with a polygenic autoimmune etiology. Out of a sample of 79 subjects, 34 subjects with known monogenic forms of autoimmunity had a lower T1D-GRS than those without a monogenic cause (41). There is a need for further study of monogenic forms of autoimmunity to better inform criteria for genetic testing and treatment plans for patients.

Identification/Diagnosis

General features that may indicate a need for genetic testing are listed in Table 1.

Clinical characteristics

Studies that use narrow clinical criteria such as a linear family history of diabetes, negative pancreatic autoantibody testing, and lack of obesity at diagnosis find a higher proportion of patients with monogenic diabetes, although there are always exceptions to these guidelines.

This allows for a more accurate probability determination of monogenic diabetes, confirmed with genetic testing, resulting in a proper treatment plan. Each monogenic form can present with distinctive clinical characteristics (Figure 1 and 2), with a few cases falling outside of the typical presentation. A 12-week-old infant who consistently tested positive for islet cell antibodies (ICA), yet has a confirmed diagnosis of a *KCNJ11* mutation (H46L), is an example of such a case (42). While examining key clinical characteristics can assist in identifying patients with MODY and infancy-onset diabetes, a patient's complete medical background and family history must be holistically taken into consideration, and ultimately a genetic test must be performed to formally diagnose a patient with a monogenic form of diabetes.

Probability calculator

The MODY probability calculator, created by the University of Exeter, can be a helpful tool to learn more about the factors that can influence a suspicion of monogenic diabetes (43). The tool calculates a Positive Predictive Value (PPV) which can vary substantially based on the BMI of the patient, current insulin treatment, and whether the patient has an affected parent. Because this tool was created based on a primarily Caucasian European population, it may not be as useful for patients from a minority race/ethnicity who may have shifted BMI curves or for the possibility of a *de novo* mutation.

Urinary C-peptide creatinine ratio (UCPCR)

UCPCR can be useful in distinguishing T1D from a monogenic form of diabetes by providing an estimate of endogenous insulin secretion in a non-invasive urine sample. One study compared 220 adult patients with diabetes duration of 5 or more years (97: known MODY, 69: T1D, 54: T2D) (44). UCPCR was significantly lower in patients with T1D than in HNF1A/HNF4A-MODY (<0.2 nmol/mol vs. 1.72 nmol/mol, $p<0.0001$) but did not distinguish from T2D. Although this method is less invasive than blood c-peptide testing, it is primarily used on a research-basis at this time.

Family history

A strong, linear family history of diabetes is common among MODY cases, although MODY patients without an affected parent have been reported (45). Diabetes is usually diagnosed under 40 years of age. While some infancy-onset cases may have an affected parent, congenital forms of diabetes are more likely to be *de novo* (7). Among patients with a GCK-MODY mutation, there is usually a strong family history of stable mild fasting hyperglycemia. Although present from birth, it can be identified at any age, most commonly during sports physicals, first pregnancies, and employee health screenings. In addition, due to changes in the standard diabetes diagnosis range, older generations may not have known about their mildly elevated blood glucose levels because it was under the clinically diagnosable level at that time. Therefore, a strong family history of diabetes should initiate further inquiry.

HNF1B mutations can cause diabetes in addition to renal cysts, renal structural defects and/or genitourinary abnormalities, which may not always occur together in each generation. Family members may exhibit renal abnormalities without a diabetes diagnosis, but still be

carriers for the mutation. So, it is important to provide genetic testing for relatives of an affected proband.

Using T1D Genetic Risk Score

A T1D genetic risk score may help to distinguish patients with likely T1D from those that may have monogenic diabetes; however, high risk T1D alleles are common and do not necessarily exclude the possibility of an underlying highly penetrant damaging mutation (46,47). This score weights 30 single nucleotide polymorphisms that have been associated with an increased risk of T1D and combines them into one score. It is important to note that this score has only been validated in Caucasian populations at this time. Additionally, these risk scores are not definitive and should therefore not be used in isolation; rather, the score is useful in selecting those least likely to have T1D for further research-based testing.

Infancy-Onset Diabetes

Diagnosis of diabetes during infancy is a unique challenge because the usual signs/symptoms are difficult to recognize in a baby; indeed, polyuria and polydipsia can be falsely reassuring. We found that the most commonly reported signs/symptoms in a sample of 88 infancy-onset patients were polyuria, tachypnea, flu-like symptoms, tiredness/weakness, dehydration and “not acting right” (48). In addition, 66% of these infants presented in DKA, and the odds of DKA increased with increasing age at diagnosis (OR per 1 month increase 1.23 [95% CI 1.04, 1.45]). A delay in diabetes diagnosis during infancy may play a role in these severe presentations.

Age at diagnosis in infancy can be helpful in differentiating between monogenic causes and polygenic T1D. Monogenic mutations are found in 80–85% of infants diagnosed under 6 months of age (7), and about 5–10% of those diagnosed between 6–12 months of age (University of Chicago Monogenic Diabetes Registry, data unpublished). We encourage genetic testing for any infant diagnosed under one year of age.

Treatment

One of the most significant outcomes of a monogenic diabetes diagnosis is the impact it may have on a patient’s treatment plan. For several types of congenital diabetes and MODY, a patient may be able to transition from insulin to oral medications or to discontinue all medical therapies. In general, we recommend confirming a genetic diagnosis before making treatment changes. The exception is in the case of a child with newly diagnosed congenital infancy-onset diabetes cases without a history of consanguinity, in which we would recommend considering a trial of SU (49). This article discusses the off-label use of generic SU drugs in children including higher than approved SU doses, in addition to the use of several forms of insulin that are considered off-label in infants.

KATP-related diabetes

Among children with a *KCNJ11* or *ABCC8* mutation, early use of sulfonylureas (SU) has been shown to dramatically improve glycemic control compared to insulin (49–51). In addition, there is evidence for improvement in neuropsychomotor impairments, visuomotor

problems, and behavior (52–54). While hypoglycemia is a common risk of SU treatment in patients with T2D, subjects with a *KCNJ11* mutation saw near-normal glycemic control with infrequent mild-moderate hypoglycemia, and no episodes of severe hypoglycemia, despite the often high dose of SU (55). High dose SU treatment is confirmed to be effective and safe as a 10-year study showed steady glycemic control and no adverse events (Bennet, yet to be published). This further supports the need for access to early genetic testing as the standard of care for infancy-onset diabetes to allow for early initiation of appropriate treatment. As clinical outcomes improve for these patients, medication management during future pregnancies may be of interest to patients and healthcare providers alike (56,57).

6q24-related transient diabetes

Historically, insulin has been the most frequently used treatment for both the infancy and reoccurrence phases of 6q24-related diabetes. Recent studies have shown that SU may be a safe and effective treatment during the infancy phase without adverse events (49,58). Similarly, adults in the recurrence phase may have preserved endogenous insulin production and may benefit from non-insulin therapies. Four adults participated in a SU trial and remained off insulin with good glycemic control at a 5 month follow up (59). Adding metformin or sitagliptin was useful in three of the cases.

INS-related diabetes and insulin therapy in infants

INS mutations resulting in infancy-onset diabetes, as well as other forms of monogenic diabetes, are very likely to require insulin therapy, similar to patients with T1D. Early identification of an *INS* mutation in one family allowed for earlier and more aggressive insulin administration, potentially leading to preserved beta-cell function (36). The use of diluted insulin or continuous subcutaneous insulin infusions are effective and safe in infants and allow for appropriate dosing of the small amounts required to maintain target blood sugars (60). Reviews of insulin management in infants, from suggested starting doses to accounting for breastmilk in carbohydrate counting, have been published (61–64).

GCK-MODY

Pharmacological treatment does not significantly change glycemic levels in patients with GCK-MODY, and thus, treatment is typically not recommended (65). One exception is in the case of a pregnant woman with GCK-MODY, depending on the mutation status and intrauterine growth of the fetus (56). A study of 117 probands with GCK mutations found that nearly 50% of subjects were inappropriately given glucose-lowering agents prior to genetic testing, with hypoglycemia as the most commonly reported side-effect (29). After a confirmed genetic diagnosis of GCK-MODY, nearly 80% of subjects ceased pharmacotherapy with no change in HbA1c levels at follow-up. This stable, mildly elevated fasting hyperglycemia has not been associated with an increase in diabetes-related complications (30). Correctly identifying GCK-MODY early is important to avoid unnecessary pharmacological risks and healthcare costs.

HNF1A- and HNF4A-MODY

Most patients with HNF1A-MODY, and many patients with HNF4A-MODY, exhibit a pronounced sensitivity to sulfonylureas (sometimes with hypoglycemia) and are able maintain target glycemic control on very small doses. Patients on insulin therapy before obtaining a correct genetic diagnosis often have poorer glycemic control (66). If additional medications are required, other non-insulin therapies such as GLP-1 receptor agonists, may be helpful in lowering glucose levels without significant risk of hypoglycemia (67). Glinide therapy has been shown to be beneficial for active adolescents, as these medications have a shorter duration of action than sulfonylureas, and thus a decreased risk for hypoglycemia (68). Recent reviews provide helpful guidance on management of HNF1A- and HNF4A-MODY during pregnancy (56,57).

HNF1B-MODY

In a large cohort of patients, 49% were treated with insulin at diabetes diagnosis, and 79% were treated with insulin at follow-up (69). Over half (57%) were responsive to SU or repaglinide shortly after diagnosis (0.75 year) for a duration of 5 years. However, switching from insulin to SU or repaglinide was only successful in 30% of patients. A separate case of a patient diagnosed at 17 years old responded well to oral medications (sitagliptin and glimepiride) for six years, after which time adding insulin was necessary (70).

Genetic testing

Genetic testing is the only way to diagnose monogenic diabetes. The results will guide personalized diabetes treatment, reveal the possibility of associated conditions, and inform inheritance risk for family members. Currently, the field is moving away from single gene targeted testing towards multigene next generation sequencing (NGS) panels (71). This testing method is more comprehensive, more efficient, and may be more cost-effective. One study found that 4 known GCK-MODY gene mutations were missed in Sanger sequencing, but identified by NGS (72). There is a trend towards even more comprehensive approaches, such as whole exome sequencing and whole genome sequencing. While these methods can provide coverage of multiple known genes, as well as allow for gene discovery in both exons and regulatory regions, dealing with the deluge of data obtained can be time-consuming and expensive.

Genetic testing has been shown to be cost-effective in certain populations, including congenital diabetes (73), those with a clinical presentation consistent with MODY (74), or if genetic testing costs decreased (75).

Although cheaper genetic testing has become more commonplace, insurance coverage continues to be a substantial hurdle, particularly in the United States. In fact, in one US study of GCK-MODY patients, over 80% received a genetic diagnosis only through participation in research, primarily due to insurance coverage issues (29). Additionally, fear of discrimination from insurance companies and difficulty with reimbursement are barriers patients have noted in seeking out genetic testing (76). Health literacy on monogenic diabetes is improving as a study found that 16 websites shared information on the most

common forms of MODY. However, there was an opportunity to improve on support resources available to patients (77).

Genetic testing is important, not only for providing a correct diagnosis today, but for providing information to extended family members and future generations. Awareness of genetic status can provide an undiagnosed family member an attributable cause for their ailment. In addition, carriers of the mutation should be given the autonomy to make informed decisions on whether or not to have offspring, and how to prepare for a possible monogenic diabetes diagnosis (78).

Conclusion

Although the study of monogenic diabetes is a fairly new field, with advancements in genetic testing technology, pharmacology, and clinical screening, there is a prodigious opportunity to positively impact the lives of people living with a monogenic form of diabetes. Utilizing a clinical screening pathway to identify patients with an atypical form of diabetes is a helpful first step. However, medical and family history should be taken into consideration on an individual level, and all clinical suspicions must be confirmed with genetic testing even if appeals for insurance coverage are required. Much of the current data on monogenic diabetes is based on Caucasian populations, and so increasing the ethnic diversity among research subjects is increasingly important to better understand the impact for all populations. As we continue to learn more about these forms of diabetes, it is crucial to effectively disseminate the findings to healthcare providers and patients alike. Continuing to expand on existing monogenic diabetes research will allow for better collaboration among scientists and participants, improved understanding of the etiology and long-term effects of these conditions, and ultimately help to inform best practices.

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morbidity including neurodevelopmental and anxiety disorders. These conditions were often previously unrecognized, suggesting that all patients with KATP-related diabetes should undergo standardized testing for such problems.

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Key points (3–5 key points/sentences that summarize your article)

1. Analyzing clinical characteristics can be an important first step to assessing the need for genetic testing.
2. High dose sulfonylurea treatment among infants with *KCNJ11* or *ABCC8*-related diabetes does not increase risk for severe hypoglycemia and has exhibited long-term effectiveness.
3. Insurance coverage of genetic testing in the United States continues to be a barrier despite the proven cost-effectiveness of testing in certain populations.
4. Further research on monogenic diabetes within ethnically and racially diverse populations will allow for more representative research data and treatment options for all populations.

Figure 1. Possible gene causes of various phenotypic characteristics of infancy-onset diabetes

*Antibody status is not definitive – monogenic cases can have positive antibodies and T1D cases can have negative antibodies. Use in conjunction with other information.

Figure 2. Possible gene causes of various phenotypic characteristics of monogenic diabetes later in life

*Antibody status is not definitive – monogenic cases can have positive antibodies and T1D cases can have negative antibodies. Use in conjunction with other information.

Table 1.

Clinical characteristics that may indicated a need for genetic testing

Infancy-onset diabetes	Diagnosed with diabetes 1 year of age
GCK-MODY phenotype	Lifelong [*] , asymptomatic, stable, mildly elevated fasting hyperglycemia (fasting blood glucose 100-140 mg/dL, HbA1c 5.6-7.8%); usually normal weight at diagnosis; negative diabetes autoantibodies
Atypical T1D	Negative diabetes autoantibodies; evidence of endogenous insulin production >3-5 years from diagnosis; usually no severe ketosis
Atypical T2D	Normal BMI at diagnosis and lacking features of metabolic syndrome (acanthosis nigricans, insulin resistance, hypertension, low HDL, high triglycerides)
Highly significant family history	Family history of diabetes occurring at a relatively young age (usually under 40 years) consistent with autosomal dominant pattern of inheritance, especially if more than 2 generations (up to 5% of T1D cases may have an affected parent, and more often in T2D)
Other special features	Diabetes with other unusual features, such as: congenital heart defect (<i>GATA4/6</i>), renal cysts and/or structural genitourinary abnormalities (<i>HNF1B</i>)

* Although the mild hyperglycemia is present from birth, it does not cause symptoms and may go unnoticed and be identified at any age, usually incidentally such as during a sports physical, employee health screening, or pregnancy.