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Monogenic Diabetes in Children and Adolescents: Recognition and Treatment Options

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Abstract

Purpose of Review—We provide a review of monogenic diabetes in young children and adolescents with a focus on recognition, management, and pharmacological treatment.

Recent Findings—Monogenic forms of diabetes account for approximately 1–2% of diabetes in children and adolescents, and its incidence has increased in recent years due to greater awareness and wider availability of genetic testing. Monogenic diabetes is due to single gene defects that primarily affect beta cell function with more than 30 different genes reported. Children with antibody-negative, C-peptide-positive diabetes should be evaluated and genetically tested for monogenic diabetes. Accurate genetic diagnosis impacts treatment in the most common types of monogenic diabetes, including the use of sulfonylureas in place of insulin or other glucose-lowering agents or discontinuing pharmacologic treatment altogether.

Summary—Diagnosis of monogenic diabetes can significantly improve patient care by enabling prediction of the disease course and guiding appropriate management and treatment.

Keywords

Monogenic diabetes; Maturity-onset diabetes of the young; Syndromic diabetes; Type 1 diabetes; Type 2 diabetes; Genetic testing

Introduction

Diabetes is characterized by hyperglycemia due to primary defects in insulin secretion and/or insulin action. The majority of diabetes can be classified as type 1 diabetes (T1D) or type 2 diabetes (T2D), both of which are complex, polygenic disorders. Monogenic forms of diabetes represent an uncommon heterogeneous group of single gene disorders primarily characterized by functional defects of pancreatic beta cells resulting in moderate to severe hyperglycemia [1, 2]. Monogenic forms of diabetes include neonatal diabetes mellitus, maturity-onset diabetes of the young (MODY), mitochondrial diabetes, and rare diabetes-associated syndromic diseases.

Conflict of Interest May Sanyoura, Louis H. Philipson, and Rochelle Naylor declare that they have no conflict of interest.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

There are now more than 30 genes found to be associated with different monogenic diabetes subtypes, many of which have provided considerable insight into molecular pathways relevant to beta cell physiology, insulin secretion, and action [3]. These gene discoveries have also led to significant improvements in patient care with several examples of personalized genomic medicine [4•, 5].

This review will cover monogenic causes of pancreatic beta cell dysfunction presenting in childhood and adolescence, with a focus on clinical presentation, recognition, treatment, and management. We will begin by discussing the approach to diagnosing monogenic diabetes in children, followed by a review of the specific clinical characteristics and treatment of several forms of monogenic diabetes.

While neonatal monogenic diabetes, which presents at birth or in infancy, is an important subtype of monogenic diabetes, it is beyond the scope of this review.

Prevalence of Monogenic Diabetes in Children and Adolescents

Several studies have systematically screened for monogenic diabetes or MODY in the pediatric population, with an estimated prevalence of 1.1–4.2% [6–10].The SEARCH for Diabetes in Youth Study, a US multicenter population-based study, identified a minimum MODY prevalence of 1.2% and a further 0.2% with neonatal diabetes [9, 11]. A systematic population screening from UK pediatric clinics reported the prevalence of monogenic diabetes in cases diagnosed under the age of 20 years as 2.5% [10••]

Recognition of Monogenic Diabetes in Children and Adolescents

Maturity-Onset Diabetes of the Young (MODY)

The term MODY was first used in the 1970s to describe heritable forms of diabetes distinct from insulin-dependent type 1 and noninsulin-dependent type 2 diabetes [12]. Now, MODY represents a clinically heterogeneous group of autosomal-dominant disorders caused by mutations in genes involved in beta cell development and insulin secretion and is the most common form of monogenic diabetes, estimated to account for 1–2% of diabetes cases (see Table 1) [13].

There is clinical overlap between MODY, type 1, and type 2 diabetes resulting in frequent misdiagnosis of MODY. The classic phenotype of MODY includes nonketotic noninsulin-dependent diabetes with diagnosis before age 25 years and an affected parent. However, several studies have shown that a substantial number of individuals with a confirmed genetic diagnosis of MODY do not fit the classic clinical description and it is estimated that > 80% of MODY cases are not diagnosed by molecular testing [14, 15]. Most reported cases of MODY also are nonobese. However, this likely represents ascertainment bias. The TODAY study reported that in a cohort of obese/overweight children and adolescents, 4.5% had pathogenic changes in MODY genes suggesting that monogenic diabetes should be considered in young children and adolescents regardless of body mass index [16••].

While family history alone does not discriminate MODY from other forms of diabetes, suspicion for MODY should be raised in children with an affected parent with diabetes, and

particularly if there are ≥ 3 consecutively affected generations. An affected parent is present in 60–90% of MODY cases compared to < 10% of children with T1D [17, 18]. Having a parent with diabetes is not a discriminator between MODY and T2D (affected parent present in > 50% of young-onset cases), although suspicion should increase if those affected are nonobese or lack metabolic features.

Biomarkers are useful to identify patients with MODY misclassified as having polygenic forms of diabetes. Biomarkers consistent with MODY include negative pancreatic autoantibodies and detectable C-peptide 3–5 years after diagnosis [19]. In the SEARCH study, children with negative autoantibodies and fasting C-peptide levels ≥ 0.8 ng/mL were screened for mutations in the three most common MODY genes—glucokinase (GCK), hepatocyte nuclear factor 1-alpha (*HNF1A*), and hepatocyte nuclear factor 4-alpha (*HNF4A*). Eight percent of the population was found to have MODY. Only 6% of these patients had been correctly diagnosed with MODY, while more than 90% of cases were misdiagnosed as T1D (36%) or T2D (51%) [9]. In the UK, systematic screening using the same biomarkers confirmed a monogenic diabetes prevalence of 2.5% and additionally suggested that half of all MODY patients do not have a genetic diagnosis [10••]. In the TODAY study, negative autoantibodies and presence of C-peptide were also used to identify appropriate patients for genetic testing in their overweight/obese pediatric cohort [16••].

Syndromic Diabetes

The several cardinal features of syndromic forms of diabetes help to prompt genetic testing, although testing is often delayed because most features develop over time rather than presenting simultaneously (see Table 2).

Therapeutic Implications of Diagnosing Monogenic Diabetes in Children and Adolescents

Earlier detection of monogenic diabetes in children and adolescents allows for personalized medicine. Treatment targeted to the genetic cause has been shown to result in improvements in glycemic control, fewer diabetes-related complications, and decreased cost and burden of treatment [20–23]. Studies have suggested that genetic testing for monogenic diabetes in appropriate populations is cost-effective [24, 25, 26••, 27]. Distinguishing between monogenic diabetes and type 1 or type 2 diabetes also has important implications with regard to surveillance of complications and associated extra-pancreatic disorders and identification of affected and at-risk family members [28–30].

Approach to Genetic Diagnosis

Genetic testing should be done to confirm a clinical diagnosis of monogenic diabetes. As the number of genes associated with monogenic forms of diabetes increases, clinicians are left with a number of test options and approaches to diagnosis. Sanger sequencing remains the gold standard to detect single base substitutions and small insertions or deletions but limits the diagnosis to a few select genes, requiring a priori suspicion of the likely affected gene. Carroll et al. (2013) proposed a diagnostic algorithm where physicians first test the more common forms of MODY (*GCK*, *HNF1A*, and *HNF4A*) and only consider the rarer forms

once those three were excluded [31]. Most commercial and clinical genetic laboratories have switched from Sanger sequencing to next-generation sequencing (NGS) approaches. Next-generation targeted sequencing panels allow for simultaneous analysis of all known diabetes-related genes in a single assay and are at a similar cost to testing a few genes by Sanger sequencing. More importantly, targeted panels may identify mutations in patients who do not present with the characteristic features of the disease [3]. One important consequence of using panels is that genetic testing results are more likely to include variants of uncertain significance. These variants are often difficult to interpret with regard to causality or disease risk and often require further patient medical information and testing of first-degree relatives to assist in the analysis. Such circumstances pose a particular challenge for physicians when it comes to understanding and communicating results to patients and in making clinical management decisions. Requesting physicians should consult with experts in monogenic diabetes when causality of variants is uncertain.

Subtypes of MODY

There are now 14 genes that have been associated with a distinct subtype of MODY, each differing in function, clinical presentation (age at onset and pattern of hyperglycemia), extra-pancreatic manifestations, risk of complications, and response to treatment (Table 1) [32]. Although pathogenic mutations in any of the 14 genes may result in MODY, mutations in *GCK*, *HNF1A*, and *HNF4A* are the most common causes of MODY, representing 52, 10, and 32% of MODY cases in the UK, respectively [15, 33]. The reported prevalence of these causes in pediatric populations varies across countries due to differences in screening recommendations for diabetes, but collectively, they account for approximately 85–90% of all MODY cases [15].

GCK MODY (Previously MODY 2)

GCK-MODY is one of the most common MODY forms with mutations in 1 in 1000 individuals. Glucokinase (encoded by the gene *GCK*) is predominantly expressed in hepatocytes and pancreatic beta cells and plays a central role in glucose metabolism (glycolysis). GCK, commonly referred to as the pancreatic beta cell glucose sensor, maintains glucose homeostasis by modulating glucose-stimulated insulin secretion in response to variations in intracellular glucose concentrations [34]. Heterozygous inactivating *GCK* mutations lead to a decreased sensitivity of pancreatic beta cells in response to increasing glucose concentrations and consequently result in an increased set point for glucose-stimulated insulin secretion. There are now more than 600 reported *GCK* mutations.

Clinical Features—The majority of patients are incidentally discovered during a routine screen and present with nonprogressive and mild fasting hyperglycemia. Fasting blood glucose is typically in the impaired fasting glucose range (98–150 mg/dl), and there is often, but not always, a small incremental rise in blood glucose during an oral glucose tolerance test (OGTT) (generally below 54 mg/dl) [35]. Glycated hemoglobin (HbA1c) is mildly elevated and ranges between 5.6 and 7.3% in those ≤ 40 years (5.9–7.6% > 40 years) [36]. Free fatty acid (FFA) levels are reduced which suggests that there may be a compensatory mechanism of increased insulin sensitivity in the setting of hyperglycemia and reduced insulin secretion. This contrasts with T2D patients whose FFA levels are usually elevated

[37]. Despite lifelong hyperglycemia, patients with *GCK* mutations have a prevalence and severity of microvascular and macrovascular complications similar to that of controls without diabetes [38].

Management—Given the mild hyperglycemia, the absence of long-term complications, and the observation that treatment with oral hypoglycemic agents or insulin does not alter glycemia, the general consensus remains that pharmacological treatment is not required except during pregnancy, where management is based on fetal genotype [39–41]. Hypoglycemia and other adverse effects were reported in 33% of subjects with GCK-MODY who were misdiagnosed and treated with glucose-lowering therapy, including insulin [42]. Diagnosis of GCK-MODY through genetic testing is essential to avoid unnecessary treatment and to identify other family members.

Given the mild phenotype, unnecessity and inefficacy of pharmacologic treatment, and lack of diabetes-related complications, GCK-MODY is better considered as a unique subgroup of genetic nondiabetic hyperglycemia rather than a subtype of diabetes. This distinction may lessen the proclivity of clinicians to prescribe pharmacologic treatment, which can cause adverse effects without benefit. It ideally will also lift employment restrictions and insurance impacts that are typical in diabetes [39].

Transcription Factors

The hepatocyte nuclear transcription factors (*HNF4A*, *HNF1A*, and *HNF1B*) regulate the expression of many genes essential for the normal development and function of the liver, gut, kidney, and pancreatic islets. In pancreatic beta cells, these transcription factors regulate the expression of the insulin gene as well as the expression of other genes involved in glucose transport and metabolism [43, 44].

HNF1A MODY (Previously MODY3)

Worldwide, HNF1A-MODY is the most common MODY type [45].

HNF1A regulates the expression of multiple genes associated with glucose metabolism, insulin production, and insulin secretion [13]. Insulin secretion in response to glucose is reduced in patients with heterozygous *HNF1A* mutations, and secretory defects worsen over time as a result of the progressive beta cell dysfunction. The role of HNF1A in upregulating the transcription and expression of the sodium-glucose cotransporter 1 (SGLT2) likely helps maintain relative euglycemia for some time. This is due to a drastic decrease in *SGLT2* expression in individuals with *HNF1A* mutations, thereby reducing glucose reabsorption through the proximal tubule of the kidney [46]. Age at diabetes onset varies from one family to another even with the same mutation and among family members as well. This is related to the location and severity of the mutations. Nonsense and frameshift mutations located in the dimerization/binding domain (exons 1–6) result in a 10-year-earlier onset of diabetes compared to missense mutations located in the transactivating domain (exons 8–10) [47].

Clinical Features—Alterations in glycemia are present before onset of overt diabetes, which generally develops in the post-pubertal period. Sixty-three percent of individuals with

pathogenic *HNF1A* mutations present with diabetes by 25 years of age {Shepherd:2001cq}. There are several laboratory features seen in HNF1A-MODY. There is a large incremental rise between fasting and 2-h blood glucose concentrations during OGTTs. Additionally, due to the reduced glucose reabsorption by the kidney, glycosuria is frequently present. High-density lipoprotein (HDL) levels are frequently elevated because of *HNF1A*'s role in lipid metabolism [48]. Despite high HDL, risk for cardiovascular disease is higher in individuals with HNF1A-MODY compared to their unaffected relatives [49]. In addition to negative pancreatic autoantibodies and positive C-peptide, high-sensitivity C-reactive protein (hsCRP) is a biomarker of HNF1A-MODY that can be used to distinguish it from type 1 and type 2 diabetes (hsCRP < 0.75 mg/l is consistent with HNF1A-MODY) [50]. Biallelic mutations in *HNF1A* have been reported to be associated with hepatocellular adenomas, either a result of two somatic mutations or a result of a germline and a somatic mutation [51, 52]. Prevalence of microvascular complications in HNF1A-MODY is strongly related to glycemic control. Patients managed appropriately have lower rates of complications [20].

Management—One of the most important and characteristic features of HNF1A-MODY is sensitivity to sulfonylureas (SU), which is the first-line treatment in HNF1A-MODY3. This has significant implications, particularly for those previously misdiagnosed with T1D, as they may be able to suspend insulin therapy and be treated with SUs, even after prolonged insulin treatment [22].Children who are on oral hypoglycemia agents or subreplacement doses of insulin can stop insulin therapy and transition directly to low-dose SUs. They should be started on a half to one tab of the lowest dose of a sulfonylurea, e.g., glyburide one half to one 1.25 mg tab). The dose can be titrated up to achieve adequate glycemic control. Those on replacement doses of insulin should decrease basal insulin by at least 50% and stop bolus insulin at the time of SU initiation.

Other treatment options include meglitinides. Nateglinide 30 mg was shown to cause less hypoglycemia in adults with HNF1A-MODY compared to sulfonylureas (glibenclamide 1.25 mg) [53]. There is a published case report on the use of repaglinide and nateglinide in adolescents with HNF1A-MODY. In this study of three adolescents, use of meglitinides was associated with no or rare hypoglycemia compared to frequent hypoglycemia on SUs, suggesting that meglitinides could be the first-line therapy for adolescents with HNF1A-MODY, ahead of SUs [54].

Glucagon-like peptide-1 (GLP-1) receptor agonists have also been shown to effectively lower glucose levels in adults with HNF1A-MODY with lower rates of hypoglycemia compared to sulfonylureas [55].

Some individuals with HNF1A-MODY may not have adequate glycemic control on SUs alone or initially good control may wane over time. This seems to be related to a delay in initiating SUs as well as weight gain [20]. The best alternative treatment regimen is not clear, but options include adding basal insulin, GLP-1 agonists, or metformin to SUs. There is a published study of SGLT2 inhibitors in HNF1A-MODY, showing an effect of increased glycosuria [56]. However, this study examined effects after a single dose (dapagliflozin 10 mg). Given that individuals with HNF1A-MODY have baseline glycosuria due to decreased SGLT2 expression, it is unclear if there would be therapeutic benefit to further increasing

glycosuria. Additionally, ketogenesis has been associated with SGLT2 inhibitors. SGLT2 inhibitors cannot be recommended in HNF1A-MODYuntil additional studies of clinical efficacy and safety are done.

Individuals with HNF1A-MODY should also be treated with statins by age 40 years due to increased cardiovascular risk [49].

HNF4A MODY (Previously MODY1)

Mutations in *HNF4A* are less common and account for 5–10% of cases in the UK [15, 57]. *HNF4A* is highly expressed in liver, kidney, intestine, and pancreatic islets. It is a key regulator of hepatic gene expression and is a major activator of *HNF1A* which in turn activates the expression of a large number of genes involved in glucose, cholesterol, and fatty acid metabolism [58].

Clinical Features—The clinical presentation of HNF4A-MODY patients is similar to that of HNF1A-MODY and is characterized by a progressive decline in beta cell function. Penetrance is variable as most carriers develop diabetes in adolescence or early adulthood (before 25 years of age), but some affected carriers do not develop diabetes until the fourth decade of life [33]. One distinct difference is that *HNF4A* mutations cause hyperinsulinemia in utero in about 50% of patients leading to significant fetal macrosomia and subsequent neonatal hypoglycemia, whereas this rarely occurs in HNF1A-MODY [59, 60]. This is generally transient, progressing to normal glycemia in childhood and subsequently to decreased insulin secretion and diabetes later in life.

HNF4A-MODYalso presents with unique extrapancreatic features, including reduced levels of HDL cholesterol, low triglyceride levels, and high low-density lipoprotein (LDL) cholesterol levels [61]. Diabetic complications occur at rates similar to types 1 and type 2 diabetes and are strongly related to glycemic control.

Management—Treatment is also with low-dose SUs, as described for HNF1A-MODY above. While to our knowledge there are not published studies of meglitinides or GLP-1 use in HNF4A-MODY, it is reasonable to assume that responsiveness would be similar to that in HNF1A-MODY.

HNF1B MODY (Previously MODY5)

HNF1B mutations account for less than 10% of all MODY cases [62, 63]. More than 50% of cases are due to large genomic rearrangements or whole gene deletions, and so genetic testing for *HNF1B* should include a method to detect such deletions. Diabetes from *HNF1B* mutations is the result of both beta cell dysfunction and insulin resistance [64]. *HNF1B* plays a crucial role in early embryonic development and is involved in the organogenesis of several tissues, including gut, pancreas, liver, lung, and kidney. As a result, *HNF1B* mutation carriers can present with developmental abnormalities in all these organs [65, 66].

Clinical Features—Mutations in *HNF1B* have a wide phenotypic spectrum, and affected individuals may present with isolated renal disease, isolated diabetes, or both. In a pediatric series, renal involvement was prevalent in *HNF1B* mutation carriers, whereas diabetes was

rare [67]. HNF1B-MODY should be suspected in children or adolescents with diabetes and renal disease even in the absence of relevant family history, as spontaneous de novo *HNF1B* gene mutations occur [68]. *HNF1B* mutations are associated with a syndrome characterized predominantly by developmental renal dysfunction, diabetes, genital tract malformation, abnormal liver function, and hyperuricemia [64, 69]. The presence of cysts is the most consistent feature of the renal phenotype, leading to the name *renal cysts and diabetes* (RCAD) syndrome. Mutations in the *HNF1B* gene have also been found in association with a variety of other renal development disorders such as renal hypoplasia and dysplasia, renal agenesis, and horseshoe kidneys. Renal involvement is often severe and frequently leads to end-stage renal failure. Abnormalities of the male and female genital tracts have also been reported and include bicornuate uterus, atresia of the vas deferens, and hemi-uterus [65, 70]. Morphologic and functional abnormalities of the exocrine pancreas include pancreas hypoplasia, pancreas calcifications, and pancreas exocrine deficiency. Several studies have shown that the expression of HNF1β is associated with cancer risk in several tumors, including hepatocellular carcinoma, pancreatic carcinoma, renal cancer, ovarian cancer, endometrial cancer, and prostate cancer [71]. Chromophobe renal cell carcinoma (ChRCC) is a rare type of kidney cancer, and recent case studies suggested that the loss of HNF1β expression may exacerbate the development of ChRCC, and thus may serve as a good diagnostic maker [72, 73]. Other features of *HNF1B*-MODY include hyperuricemia (and associated gout), abnormal liver function tests, and hypomagnesemia. Early-onset hyperparathyroidism was also observed in several patients with HNF1β mutations or deletions [74]. Autism and cognitive impairment have been suggested to be a possible manifestation associated with *HNF1B* deletions [75, 76]. However, Clissold et al. reported that 17q12 deletions which encompass 14 genes including *HNF1B*, and not *HNF1B*, intragenic mutations in isolation are associated with neurodevelopmental disorders [77].

Management—Some patients may respond well to sulfonylureas or to meglitinides; however, the majority of these patients are treated with insulin.

Rarer Types of MODY

PDX1 MODY (Previously MODY4)

The homeodomain protein insulin promoter factor 1 (*IPF1*) gene, also known as pancreatic duodenal homeobox factor 1 (*PDX1*), encodes a key transcription that critically regulates early pancreatic development and multiple aspects of beta cell differentiation, maturation, and function. *PDX1* also directly regulates expression of the insulin gene and other components of the glucose stimulated insulin secretion pathway [78, 79].

Clinical Features—Mutations in *PDX1* represent a rare subtype of monogenic diabetes and are associated with several disorders, including pancreatic agenesis (or congenital pancreatic hypoplasia), permanent neonatal diabetes, or MODY. Age at onset of diabetes occurs later than that of other forms of MODY (range 17–67 years) and affects both obese and nonobese patients [80]. Clinical phenotypes range from impaired glucose tolerance to overt noninsulin-dependent diabetes with a wide variety of therapeutic responses. Other variants in *PDX1* have also been reported in pedigrees with late-onset T2D [81].

Management—Patients are either treated with diet alone, or oral hypoglycemic agents, and/or insulin.

KCNJ11, ABCC8, and INS-MODY

Mutations in *KCNJ11*, *ABCC8*, and *INS* most commonly cause neonatal diabetes but can be rare causes of MODY. Neonatal diabetes mellitus is the term commonly used to describe diabetes with onset before 6 months of age. Collectively, they account for less than 1% of all MODY cases.

KCNJ11 and ABCC8—The *ABCC8* and *KCNJ11* genes encode the sulfonylurea receptor 1 (SUR1) and inward rectifier potassium channel Kir6 (Kir6.2) subunits of the ATP-sensitive potassium (K_{ATP}) channel in the pancreatic beta cell, regulating insulin secretion. They have been associated with a spectrum of insulin secretion abnormalities [82–84].

Clinical Features: Mutations in *KCNJ11* and *ABCC8* have been reported in patients with clinical features similar to those with HNF1A or HNF4A-MODY [85, 86].

Management: These patients can also be treated with SUs [87].

INS—Depending on the position and nature of heterozygous *INS* mutations, disease phenotypes may be associated with a slow and progressive loss of insulin secretory capacity that presents later in childhood [88].

Clinical Features: While in some cases individuals present with islet antibody-negative diabetes (also known as type 1B diabetes), there are reports of several families who carry heterozygous *INS* missense mutations that cosegregate with a MODY phenotype [88–91].

Management: Some patients are initially managed with diet, but insulin is the most common treatment [88, 91].

There are other genes that have been implicated in MODY and are routinely screened in MODY diagnostic panels (see Table 1).However, each has been reported in a limited number of families and the genetic evidence is not always convincing. Still, a significant percentage of children and adolescents with autosomal dominant noninsulin-dependent diabetes have no causative gene identified (MODY-X). As the technological advancements of next-generation sequencing methods improve while costs steadily decrease, it is hopeful that novel monogenic forms of diabetes will be identified in these patients.

Syndromic Diabetes

Syndromic forms of diabetes are rare, accounting less than 1% of children seen in diabetes clinics [92]. As they are rare and quite complex, most cases are either misdiagnosed or not diagnosed at all. The importance of correctly identifying such syndromes for children lies in the anticipation, recognition, and treatment of associated complications, and for the parents, the option of genetic counseling. Here, we discuss the most common syndromic forms that

may be encountered in pediatric clinics. Additional syndromic forms and their underlying genetic cause can be found in Table 2.

Maternally Inherited Diabetes and Deafness (MIDD)

Maternally inherited diabetes and deafness (MIDD) results from an A to G substitution at position 3243 (m.3243A>G) of the mitochondrial DNA encoding the gene for $tRNA^{Leu}$ and is estimated to affect up to 1% of patients with diabetes [93, 94]. Mitochondrial dysfunction in the highly metabolically active pancreatic islets is thought to result in gradual deterioration of beta cell function, loss of beta cell mass, and decreased glucose-induced insulin release [95, 96]. Other mitochondrial DNA point mutations have been associated with MIDD, but these are extremely rare compared with the proportion of diabetes caused by m.3243A>G [97].

Clinical Features

The penetrance of diabetes in MIDD is high in carriers of the m.3243A>G mutation with a variable age of onset; the average age is35to 40years with a range of11 to 68 [94, 98]. The clinical picture of MIDD of depends mainly on the amount of heteroplasmy in beta cells. Diabetes usually presents similarly to T2D, but approximately 20% present acutely, with ketoacidosis and, therefore, cases are misdiagnosed as T1D [98, 99]. Most do not have islet cell or GAD antibodies; however, they have been detected in a small subset of patients [100, 101].

Management

Hyperglycemia is often mild, and the majority of MIDD patients are initially treated with diet or glucose-lowering agents. However, due to the progressive nature of the disease, insulin is usually required within 2 years after diabetes is diagnosed [98, 99].

Wolfram Syndrome

The most frequent syndromic form of monogenic diabetes in children and adolescents is Wolfram syndrome (WFS). Wolfram syndrome, also known as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), is a rare autosomal recessive disorder with an estimated prevalence of 1 in 770,000 [102]. Diabetes in WFS patients is a nonautoimmune type of diabetes yet is associated with insulin deficiency due to selective loss of pancreatic beta cells and impaired insulin secretion [103]. Recently, a missense change was reported to be associated with dominantly inherited non-syndromic adult-onset diabetes [104].

Clinical Features

The minimal clinical criteria for diagnosis are juvenile-onset diabetes and optic atrophy, but patients may also develop diabetes insipidus, sensorineural deafness, renal tract abnormalities, and neuropsychiatric disorders [105]. Even though the presence of visual abnormalities accompanying diabetes in patients with WFS may lead to a misdiagnosis of T1D with diabetic retinopathy in some children and adolescents, the clinical courses of these

two types of diabetes are different. Patients with WFS are autoantibody negative and are characterized by lower daily insulin requirements, low frequency of ketoacidosis, better glycemic control, and lower HbA1c levels in comparison to patients with T1D [106–108].

Management

Patients require insulin treatment from the time of diagnosis.

Alström Syndrome

Alström syndrome is a recessive monogenic ciliopathy characterized by cone-rod retinal dystrophy, childhood obesity, T2D, and sensorineural hearing loss.

Clinical Features

In the first 5 years of life, almost all patients develop truncal obesity, insulin resistance, hyperinsulinemia, and hyperlipidemia. These symptoms may progress to T2D accompanied by acanthosis nigricans [109]. Other clinical features include dilated cardiomyopathy, hepatic and renal dysfunction, hypertension, hypothyroidism, hypogonadism, urological abnormalities, short stature in adulthood, and skeletal anomalies [110, 111]. A differential diagnosis should include Bardet-Biedl syndrome, which has similar clinical features of Alström syndrome.

Management

There is no specific treatment for Alström syndrome, but early diagnosis and medical intervention can prevent or delay progression of the disease and improve quality of life.

Conclusion

Identification of monogenic forms of diabetes among children and adolescents remains a challenge, and as a result, these conditions are largely underdiagnosed with missed opportunities for genetically targeted management. Factors contributing to misdiagnosis include clinical and genetic heterogeneity of the different subtypes, clinical overlap with the more common polygenic forms of diabetes, high cost of commercial genetic testing, lack of insurance coverage, and limited knowledge of the condition by health care professionals. However, combining biomarkers with phenotype is a promising approach to lead to a more timely accurate genetic diagnosis.

Even though monogenic forms of diabetes are uncommon overall, the clinical implications of the diagnosis for the individual and their family support the use of genetic testing in appropriate cases. In particular, the absence of the classic features of type 1 or type 2 diabetes, early onset, family history, and presence of extrapancreatic features should warrant consideration of an underlying genetic form of diabetes. Raising awareness of monogenic diabetes and making the diagnosis more accessible will improve disease prognosis and disease management in children and their families.

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Table 1

Clinical characteristics of maturity onset diabetes of the young (MODY) genetic subtypes

MODY type	Gene name (locus)	Protein function	Prevalence	Other features	Treatment	OMIM[a]
MODY 1	*HNF4A* (20ql2)	Transcription factor	5–10%	Neonatal hyperinsulinemia and hypoglycemia with associated macrosonria, low serum levels of cholesterol	Sensitive to sulfonylureas	125850, 600281
MODY 2	*GCK* (7pl3)	Glycolytic enzynre	30–60%	Mild fasting hyperglycemia throughout life, often asymptomatic, gestational diabetes, low birth weight (with unaffected mother)	No treatment outside of pregnancy	138079,125851
MODY 3	*HNFIA* (12q24.2)	Transcription factor	30–60%	Glycosuria	Sensitive to sulfonylureas	600496,142410
MODY 4	*PDX1* (13ql2.1)	Transcription factor	<1%	Homozygote: pancreatic agenesis	Diet, OAD, or insulin	606392,600733
MODY 5	*HNFIB* (17q21)	Transcription factor	5–10%	Diabetes in association with renal and genito-urinary abnomralities	Insulin	137920, 189907
MODY 6	*NEUROD I* (2q31.3)	Transcription factor	<1%	Obesity and insulin resistance	OAD or insulin	606394, 601724
MODY 7	*KLF11* (2p25)	Transcription factor	<1%	Impaired glucose tolerance to overt diabetes	OAD or insulin	603301,610508
MODY 8	*CEL* (9p34)	Lipase enzynre	< 1%	Diabetes and pancreatic exocrine. Endocrine deficiency	OAD or insulin	114840,609812
MODY 9	*PAX4* (7q32)	Transcription factor	< 1%	Ketosis prone diabetes	Diet, OAD, or insulin	167413,612225
MODY 10	*INS* (llpl5.5)	Homrone	<1%	May result in neonatal diabetes, antibody-negative diabetes, and MODY	OAD or insulin	613370, 176730
MODY 11	*BLK (8p23)*	Tyrosine kinase	<1%	Obesity common	Diet, OAD, or insulin	191305, 613375
MODY 12	*ABCC8* (llpl5.1)	SURI (KATP channel regulatory subunit)	<1%	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas	600509
MODY 13	*KCNJ11* (1 lp 15.13	Kir6.2 (KATP channel regulatory subunit)	<1%	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas	616329, 600937
MODY 14	*APPL1* (3pl4.3)	Serine/threonine kinase	<1%	Adult-onset diabetes	Diet, OAD, or insulin	616511, 604299

ABCC8 ATP-binding cassette, subfamily C (CFTR/MRP), member 8, *APPL1* adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1, *BLK* B lymphocyte kinase, *CEL* carboxyl ester lipase enzyme, *GCK* glucokinase, *HNF1A* hepatocyte nuclear factor-lα, *HNF1B* hepatocyte nuclear factor-lβ, *FLNF4A* hepatocyte nuclear factor-4α, *INS* preproinsulin, *KATP* ATP-sensitive potassium channel, *KCNJ11* potassium channel, inwardly rectifying subfamily J, member 11, *KLF11* Kriippel-like factor 11, *NEUROD 1* neurogenic differentiation factor 1, *OAD* oral anti-diabetic, *PAX4* paired box gene 4, *PDX1* pancreas/duodenum homeobox protein 1, *SURI* sulfonylurea receptor 1

[a]The Online Mendelian Inheritance in Man (OMIM; http://omim.org) numbers indicate the descriptive entry of the phenotype and/or gene

Table 2

Syndromic forms of diabetes that may present in childhood or early adulthood

Syndrome	Gene (locus)	Inheritance	Type of diabetes	Clinical features	OMIM[a]
Diabetes and deafness	Mitochondria tRNA	Maternal	Insulin deficient	Adult-onset diabetes, sensorineural deafness	590050
Wolfram syndrome 1	*WFS1* (4p16)	AR/AD	Insulin deficient	Childhood-onset diabetes, optic atrophy, deafness, diabetes insipidus	600424, 606201
Wolfram syndrome 2	*CISD2* (*4q24*)	AR	Insulin deficient	Childhood-onset, diabetes, optic atrophy deafness, and defective platelet aggregation	604928, 611507
Thiamine-responsive megaloblastic anemia syndrome	*SLC19A2* (1q23)	AR	Vitamin dependent	Childhood-onset diabetes, megaloblastic or sideroblastic anemia, sensorineural deafness	249270, 600424
Mitchell-Riley syndrome	*RFX6* (*6q22*)	AR	Insulin deficient	Rare cases with childhood-onset, pancreatic hypoplasia, intestinal atresia, and gallbladder aplasia or hypoplasia	615710, 612659
Alström syndrome	*ALMS1* (2p13)	AR	Insulin resistant	Childhood-early adulthood, pigmentary retinopathy, deafness, obesity, dilated cardiomyopathy	203800, 606844
Bardet-Biedl Syndrome	*BBS1–BBS21*	AR/DR	Insulin resistant	Childhood–early adulthood, developmental delay, pigmentary retinopathy, polydactyly, obesity, hypogonadism	209900
Insulin resistance syndrome Type A	*INSR* (19p13)	AD/AR	Insulin resistant	Childhood-early adulthood, obesity, diabetes, and acanthosis nigricans	610549, 147670

ALMS1 Alström syndrome 1, *AD* autosomal dominant, *AR* autosomal recessive, *BBS* Bardet-Biedl, *CISD2*, CDGSH iron sulfur domain 2, *DR* digenic recessive, *INSR* insulin receptor, *RFX6* regulatory factor X 6, *SLC19A2* solute carrier family 19 member 2, *tRNA* transfer RNA, *WFS1* wolframin

[a]The Online Mendelian Inheritance in Man (OMIM; http://omim.org) numbers indicate the descriptive entry of the phenotype and/or gene