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Monogenic diabetes in children

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Abstract
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.

Keywords: Monogenic diabetes, Maturity-onset diabetes of the young, Syndromic diabetes, Diagnostic evaluation, diabetes

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. 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.

Diabetes

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes from the food you eat. Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy.

Therapeutic implications of diagnosing monogenic diabetes in children

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.

Prevalence of Monogenic Diabetes in Children

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 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].

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].

Conclusion

Because monogenic diabetes is a genetically heterogeneous group of disorders, selection of appropriate gene(s) to test is challenging when based solely on clinical grounds. Pathogenic variants within several genes can present with similar phenotypic characteristics, while other features that are more gene specific may not yet have manifested at the time of initial presentation with hyperglycemia. 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.

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