CLINICAL VIGNETTE

A Case of Monogenic Diabetes Secondary to Glucokinase Mutation

Amy Chow, MD and Lauren Beshay, MD

Case Report

An 18-year-old female with prediabetes and a BMI 26 kg/m^2 presents with newly diagnosed diabetes with fasting glucose of 115 mg/dl and A1C of 6.7. She was diagnosed with prediabetes two years prior and was started on metformin without much effect on her blood glucose. She adheres to a low carbohydrate diet and exercises regularly. She denies polyuria, polydipsia, polyphagia, or weight loss. She is not on any medications and has no known medication allergies. Her initial physical exam is notable for body weight of 163 lbs. and BMI of 26.31 kg/m^2. Her family history is significant for diabetes in her mother and father who were both diagnosed in their thirties. Her maternal grandmother and grandfather were also diagnosed with diabetes in their forties. Her younger brother has prediabetes. None of these family members are overweight or obese and they have no known complications of diabetes. Given her clinical history and family history, maturity onset diabetes of the young (MODY) was suspected. Her MODY genetic panel was positive for Glucokinase (GCK) heterozygous missense mutation confirming the diagnosis of MODY-GCK also known as MODY2. Pancreatic autoantibodies tests were negative for Glutamic acid decarboxylase antibody <5 IU/ml (0.0 to 5.0 IU/ml), IA 2 autoantibody < 5.4 U/ml (0.0-7.4 U/ml), insulin antibody < 0.4 U/ml (0.0 to 0.4 U/ml), zinc 8 transporter Antibody < 10.0 U/ml (0.0 to 15.0 U/ml). Continuation of lifestyle modification and weight loss counseling were recommended.

Discussion

MODY is a disorder characterized by noninsulin-dependent diabetes diagnosed at a young age (<25 years) with autosomal dominant inheritance and lack of autoantibodies.[1] It accounts for 2 to 5 percent of diabetes cases.[2,3] Several different genetic abnormalities have been identified causing disruption in pancreatic beta cells development and function leading to impaired insulin secretion.[4] Mutations in hepatocyte nuclear factor-1-alpha (HNF1A) and the GCK gene are the most commonly identified mutations, occurring in up to 65 and 32 percent of MODY cases.[5,6] MODY-GCK is characterized by a mild course and low risk of chronic diabetes complications [7].

More than 30 pathologic variants of the GCK gene on chromosome 7 have been described.[8] GCK phosphorylates glucose to glucose-6-phosphate in the first step of glycolysis in both hepatic and pancreatic beta cells.[7] In pancreatic cells, it also acts as a glucose sensor, resulting in glucose-stimulated insulin release.[7] A pathogenic variant in the GCK gene causes a higher threshold for insulin secretion.[7] The resulting hyperglycemia is often mild, and therefore not associated with the vascular complications common in other types of diabetes.[7] Patients with MODY-GCK can often be managed with lifestyle modifications alone.[7]

There are no defining features that are pathognomonic for MODY-GCK. Patients typically are diagnosed with diabetes at a young age, with asymptomatic fasting hyperglycemia (100-150 mg/dl), and lack the autoantibodies seen typically in type 1 diabetes.[9] They have only a mild increase in hemoglobin A1c within the range of 5.6–7.6.[9] The level of hyperglycemia in MODY-GCK is not high enough to exceed the renal threshold, avoiding the osmotic symptoms of polyuria, polydipsia, and weight loss. Therefore, most patients are diagnosed incidentally via mild hyperglycemia found at a health screening in an asymptomatic individual, or at admission to a hospital for a different condition.[10]

Genetic testing for monogenic diabetes should be considered in any of the following scenarios: 1) multigenerational family history of diabetes (≥3 generations or history in one parent and at least one other first-degree relative of that parent) with other clinical characteristics described above and negative autoantibodies[11]; 2) a high probability of monogenic diabetes (>25 percent in people not treated with insulin) using the MODY Clinical Risk Calculator[12]; and 3) in individuals with presumed type 1 diabetes with preserved fasting C-peptide (>0.6 ng/mL when glucose is >72 mg/dL) three to five years after initial presentation.[12]

MODY-GCK is identified in about 1% of women with gestational diabetes during glycemic screening at 24th to 28th gestational weeks.[12] In pregnancy, management depends on the fetal genotype. If the fetus inherits the maternal GCK variant (which will prevent fetal hyperinsulinemia and excessive growth despite maternal hyperglycemia), maternal hyperglycemia does not require treatment.[12] However, if the fetus does not inherit the pathogenic variant, maternal insulin therapy is indicated to prevent excessive fetal growth.[12] Thus, when available, noninvasive prenatal genotyping with cell free DNA should be used to guide management of GCK-MODY during pregnancy.[12]

Conclusion

It is important to distinguish MODY-GCK from type 1 diabetes and type 2 diabetes because the optimal treatments and risks for diabetes complications are different. An accurate diagnosis of MODY-GCK allows earlier identification of at-risk family members due to autosomal dominant inheritance. A suspected diagnosis of MODY-GCK should be confirmed by genetic testing.

REFERENCES

1. **Tattersall RB, Fajans SS**. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes*. 1975 Jan;24(1): 44-53. doi: 10.2337/diab.24.1.44. PMID: 1122063.
2. **Gat-Yablonski G, Shalitin S, Phillip M**. Maturity onset diabetes of the young --review. *Pediatr Endocrinol Rev*. 2006 Aug;3 Suppl 3:514-20. Erratum in: *Pediatr Endocrinol Rev*. 2007 Sep;5(1):470. PMID: 17551475.
3. **McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, Williams A, Hattersley AT, Ellard S**. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. *Diabet Med*. 2011 Sep;28(9):1028-33. doi: 10.1111/ j.1464-5491.2011.03287.x. PMID: 21395678.
4. **Naylor R, Philipson LH**. Who should have genetic testing for maturity-onset diabetes of the young? *Clin Endocrinol (Oxf)*. 2011 Oct;75(4):422-6. doi: 10.1111/j.1365-2265. 2011.04049.x. PMID: 21521318.
5. **Fajans SS, Bell GI, Polonsky KS**. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med*. 2001 Sep 27;345(13):971-80. doi: 10.1056/NEJMra002168. PMID: 11575290.
6. **Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S**. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia*. 2010 Dec;53(12):2504-8. doi: 10.1007/s00125-010-1799-4. Epub 2010 May 25. PMID: 20499044.
7. **Hulín J, Škopková M, Valkovičová T, Mikulajová S, Rosoľanková M, Papcun P, Gašperíková D, Staník J**. Clinical implications of the glucokinase impaired function - GCK MODY today. *Physiol Res*. 2020 Dec 22;69(6):995-1011. doi: 10.33549/physiolres.934487. Epub 2020 Nov 2. PMID: 33129248; PMCID: PMC8549873.
8. **Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F, Lesage S, Stoffel M, Takeda J, Passa P, et al**. Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. *N Engl J Med*. 1993 Mar 11;328(10):697-702. doi: 10.1056/NEJM 199303113281005. PMID: 8433729.
9. **Chakera AJ, Steele AM, Gloyn AL, Shepherd MH, Shields B, Ellard S, Hattersley AT**. Recognition and Management of Individuals With Hyperglycemia Because of a Heterozygous Glucokinase Mutation. *Diabetes Care*. 2015 Jul;38(7):1383-92. doi: 10.2337/dc14-2769. PMID: 26106223.
10. **Velho G, Blanché H, Vaxillaire M, Bellanné-Chantelot C, Pardini VC, Timsit J, Passa P, Deschamps I, Robert JJ, Weber IT, Marotta D, Pilkis SJ, Lipkind GM, Bell GI, Froguel P**. Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. *Diabetologia*. 1997 Feb;40(2):217-24. doi: 10.1007/s001250050666. PMID: 9049484.
11. **Greeley SAW, Polak M, Njølstad PR, Barbetti F, Williams R, Castano L, Raile K, Chi DV, Habeb A, Hattersley AT, Codner E**. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2022 Dec;23(8):1188-1211. doi: 10.1111/pedi.13426. PMID: 36537518; PMCID: PMC10107883.
12. **Ashok B, David MN, Joseph IW et al.** Classification of diabetes mellitus and genetic diabetic syndromes. In: *UpToDate*, Post, TW (Ed), UpToDate, Waltham, MA, 2024.