

Mild Fasting Hyperglycemia in a Child: Importance of New Genetic Tools

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The last 2 decades have witnessed a much better understanding of monogenic diabetes (commonly referred to as *mature onset diabetes of the youth* or MODY). Such diabetes results from dominantly or recessively inherited, or a de novo genetic mutation with subsequent dysregulation of insulin secretion by the pancreatic beta-cells.¹

It is estimated that monogenic diabetes accounts for 1% to 2% of diabetes cases, and it is often misdiagnosed as type 1 or type 2 diabetes. A timely diagnosis of monogenic diabetes will predict clinical course, explain associated features, and guide therapy of the index case as well as other diabetic family members.²

At least seven single-gene mutations have been described to be associated with monogenic diabetes with more candidate genes being investigated for other types of monogenic diabetes. MODY2 accounts for about 20% of cases of monogenic diabetes. It is caused by heterozygous loss of function in glucokinase, the enzyme that catalyzes the first step of glucose metabolism in the pancreatic beta-cells. This leads to regulation of glucose at a higher set point with non-deteriorating mild fasting hyperglycemia.³ Treatment is not usually required, as microvascular or macrovascular complications have been rarely described. Administration of insulin

results in reduction of endogenous insulin secretion with no change of glycemic status (see case discussion).

As genetic testing for monogenic diabetes is currently commercially available (Table 1), clinicians now are able to accurately confirm such diagnosis. The following case illustrates the importance of considering this diagnosis in children with asymptomatic mild fasting hyperglycemia with family history of diabetes and lack of evidence of autoimmunity against the pancreatic beta-cells.

CASE DISCUSSION:

A 10-year-old Caucasian girl was seen at her pediatrician office for a routine physical exam. A urinalysis revealed isolated glycosuria, and a random serum glucose was 153 mg/dL. She had no symptoms suggestive of diabetes. Her pediatrician obtained an oral glucose tolerance test with the following blood glucose: 102, 174, 216, 233, and 195 mg/dL at 0, 30, 60, 90, and 120 minutes, respectively. A1C at the local hospital laboratory was 6.3%. Her past medical history was unremarkable except for allergic rhinitis, which was treated with montelukast sodium (Singulair, Merck & Co., Inc.), mometasone furoate monohydrate (Nasonex, Schering Corporation), and loratadine (Claritin, Schering-Plough Corporation). Her paternal uncle and grandmother

TABLE 1. CURRENT AVAILABLE MODY GENETIC TESTS BY ATHENA DIAGNOSTICS

MODY Subtype	Affected Gene	Affected Protein	Prevalence in the US and Europe
MODY1	HNF4A	hepatocyte nuclear factor 4	uncommon
MODY2	GCK	glucokinase	common
MODY3	HNF1A	hepatocyte nuclear factor 1	most common
MODY4	IPF1	insulin promoter factor 1	uncommon
MODY5	HNF1B	hepatocyte nuclear factor 1	uncommon
MODY8	CEL	carboxyl ester lipase	very rare

TABLE 2. METER BLOOD GLUCOSE READINGS (MG/DL) OF INDEX CASE AND HER FATHER^a

Index Case				Father
With Insulin		Without Insulin		No Treatment
Fasting	Bedtime	Fasting	Bedtime	Fasting
118	132	107	116	115
123	117		135	122
105	127		133	112
105	141		141	108
106	135		117	104
115	118		149	
110	155	113		
112	163	111	145	130
128	159		147	119
122	155	103		110
119	106		124	105
114	133		135	121
132	142		128	123
107	150		133	125
120	154	110		101

^aTreatment with insulin led to reduction of endogenous insulin with maintenance of glycemic status and no hypoglycemia. Monitoring of her father's blood glucose revealed undiagnosed mild fasting hyperglycemia.

have a history of mild type 2 diabetes, and her father has hypothyroidism.

The patient was referred to a pediatric endocrinologist for further evaluation. She had a normal exam with a weight of 42.6 kg, height of 151.9 cm, and body mass index of 18.4 kg/m². Human insulin, islet cell antigen 512 and antiglutamic acid decarboxylase 65 antibodies were negative. She was started on 5 units of glargine insulin (Lantus, Sanofi Aventis) daily. She did not require insulin coverage for her meals giving her mild hyperglycemia (Table 2). After 6 months, her glycemic control remained unchanged with an office A1C of 5.8%.

Her presentation, clinical course, and family history raised the possibility of monogenic diabetes. Genetic evaluation through Athena Diagnostics (Worcester, MA) revealed heterozygous p.His317Gln mutation of the glucokinase gene consistent with the diagnosis of monogenic diabetes MODY2.

The patient's insulin was stopped without change of her blood glucose (Table 2). Healthy diet and scheduled physical activity were recommended. Her father was asked to check his blood glucose and was found to have mild fasting hyperglycemia consistent with an autosomal dominant pattern of MODY2 (Table 2). She continued to be asymp-

tomatic 1 year after stopping insulin with unchanged A1C of 5.8 %.

CONCLUSION

The recent advances and availability of genetic testing for monogenic diabetes represent an important tool for clinicians who take care of diabetic patients as monogenic diabetes accounts for 1% to 2% of the diabetic population. Making the right diagnosis will have valuable prognostic and therapeutic implications. The discussed case illustrates how such diagnosis saved this child and her family years of psychological, physical, and economic burden of otherwise unnecessary treatment. ■

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