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Incidental cause of mild hyperglycemia in children: Genetic, clinical, and follow-up features of glucokinase-MODY diabetes

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Abstract

Aim: This study aimed to present the genetic, clinical, and follow-up data of our patients diagnosed with glucokinase (GCK)-MODY. Type 2 Maturity Onset Diabetes of the Young (MODY) is a monogenic disease characterized by fasting hyperglycemia resulting from impaired insulin secretion. It constitutes the vast majority of cases with monogenic diabetes.

Materials and Methods: In the study, clinical, follow-up, and genetic data of 13 patients who were followed up with the diagnosis of MODY type 2 diabetes and had mutations in the GCK gene in their molecular analyses were studied. GCK whole gene sequence analysis was performed with Sanger sequencing.

Results: The age at diagnosis was median 11.0 years (range: 2.5–16.9). High blood sugar was the most common reason for admission (84.6%). At the time of diagnosis, the patients' mean blood sugar was 137.0±52.4 mg/dL, insulin 6.1±2.8 mU/L, c-peptide 1.4±0.6 ng/mL, triglyceride 106.1±42.3 mg/dL, and cholesterol 154.0±19.0 mg/dL. While HbA1c was 6.3±0.4 at the time of diagnosis, it was 6.2±0.4 at the end of the mean 5-year follow-up (p=0.073). Molecular analysis revealed the most common variant as c.565A>G (p.I189Val) (53.8%). In all cases, glucose levels were regulated by diet and exercise, and there was no need for insulin.

Conclusion: Incidental blood glucose elevation was an important finding in diagnosing GCK-MODY. With the molecular diagnosis of these patients, clinical follow-ups, treatment plans, and long-term prognoses can be planned more accurately. Therefore, in doubtful cases, the genetic diagnosis should be confirmed by sequencing the GCK gene.

Introduction

Although monogenic diabetes is rarer than type 1 and 2, they appear to be common. There is no definitive literature data on its prevalence, but it is thought that 1-5% of all diabetics are monogenic [1,2]. In most cases of monogenic diabetes, mutations are inherited in an autosomal dominant manner. However, it may also occur sporadically to a lesser extent. The glucokinase (GCK) gene was the first identified Maturity Onset Diabetes of the Young (MODY) gene. Glucokinase is an enzyme that converts glucose to glucose 6-P and plays a key role in glucose metabolism. The GCK gene encodes a protein with 12 exons, a molecular weight of 52.191 Da, and 465 amino acids in the 7p15.3-7p15.1 region on the 7th chromosome [3]. GCK functions as a glucose sensor of pancreatic beta cells. GCK activity is primarily related to blood glucose concentration and plays a direct role in controlling insulin secretion. Additionally, glucokinase stimulates glycogen synthesis in the liver and insulin release in beta cells [1-3].

It is not always easy to distinguish MODY-2 clinically from type 1 and 2 diabetes. For this reason, many patients who cannot be diagnosed with MODY-2 can be misdiagnosed and treated. Although MODY-2 constitutes a very small portion of all diabetic cases, monogenic diabetes should be suspected in patients with type 1 and 2 diabetes but with an atypical course; and in type 1 diabetes patients without autoantibody positivityand the diagnosis should be confirmed with appropriate molecular tests [1-4]. It is thought that there is no increase in the risk of microvascular and macrovascular complications associated with long-term diabetes, which is the main cause of morbidity and mortality in MODY-2 cases [1].

Persistent hyperinsulinemic hypoglycemia was seen in newborns and infancy with glucokinase gene activating mutations, MODY type 2 resulting from heterozygous in-

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activating mutations of the glucokinase gene, and permanent neonatal diabetes due to homozygous inactivating mutations [5]. While investigating the etiology of permanent neonatal diabetes in Turkey and in societies where consanguineous marriage is common, homozygous mutations in the GCK gene should also be considered. It is the most common type of MODY in Turkey [6,7]. In our study, we aimed to determine the molecular and clinical features of GCK-MODY patients. In addition, after a mean follow-up of 5 years, HbA1c and treatment protocols were evaluated.

Materials and Methods

Subjects

Thirteen patients who were clinically diagnosed with GCK MODY from the pediatric endocrinology center and had mutations in the GCK gene were included. The study was approved by the Malatya Training and Research Hospital Ethics Committee (23536505-000-4044). Before starting the study, the aim and scope of the study were explained by interviewing the parents. Written informed consent was obtained from the patient's legal guardians. Demographic characteristics, laboratory findings, age at diagnosis, medical records, and family members of the patients were examined, and pedigrees containing at least three generations were drawn. Anthropometric measurements and physical examination findings were evaluated. A Harpenden stadiometer (with 0.1 cm sensitivity) was used for height measurements. Weight was measured via a SECA scale (Model 803, Seca™, Hamburg, Germany) (with a 0.1 kg sensitivity). BMI was calculated using Bodyweight (kg)/Height^2 (m^2).

Biochemical analysis

Samples were taken from the patients for fasting blood glucose, total serum cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), c-peptide, and insulin levels after at least 8-12 hours of fasting. In addition, laboratory results, including hemoglobin A1c (HbA1c) percentage, diabetes autoantibodies such as anti-glutamic acid decarboxylase antibody (GAD), insulin antibody (IAA), and islet cell antibody (ICA), were recorded from patient files. Diabetes is diagnosed in 3 ways: 1- when the fasting blood sugar is ≥126 mg/dl, 2- when the 2nd-hour blood sugar is ≥200 mg/dl in the oral glucose tolerance test (OGTT), and 3- when the random blood glucose is ≥200 mg/dl with classic symptoms of diabetes (polyuria, polydipsia, nocturia, enuresis, weight loss, polyphagia). The glucose oxidase method was used for blood glucose measurement, and lipid measurement was performed using the Olympus AU 2700 device. Insulin level was measured with the electrochemiluminescence method on the Roche Modular Analytics E-170 immunoassay analyzer (Roche Diagnostics, USA).

Molecular analysis

DNA isolations were made from 200 µl peripheral blood samples using the whole blood genomic DNA Isolation Kit (QIAGEN® (Hilden, Germany)) and stored at -200 C until the next step. All coding exons and exon-intron junctions of the GCK gene were PCR amplified, and whole gene Sanger sequencing was performed on the 16-capillary ABI 3130xl Genetic Analyzer. To distinguish between mutation and polymorphism for the detected variants, mutation probabilities were investigated by performing segregation analyses in families with in silico analysis systems such as Provean, Sorting Intolerant from Tolerant, Polyhen, and Mutation Taster. According to guidelines published in 2015, variants are classified as "pathogenic", "possibly pathogenic", "unknown significance", "probably benign" and "benign" [8]. Variants detected according to the criteria specified in this standard terminology were evaluated.

Statistical analysis

All data were evaluated using the SPSS 17.0 (SPSS, Inc, Chicago, Illinois, USA) statistical program. First, descriptive statistics were made for all study data. Descriptive statistics were given as mean, standard deviation, and minimum and maximum values. Then, the Paired Samples t-test was used to compare mean HbA1c at diagnosis and 5 years later. Statistical significance was taken as $p < 0.05$.

Results

MODY-2 was diagnosed in 13 cases from 11 families. There was parental consanguinity in 4 families. Patients' median age at diagnosis was 11.0 years (range: 2.5–16.9 years). The most common reason for admission was high blood sugar in 11 cases and a history of MODY in 2 of their siblings. The mean follow-up period of the cases was 5.6±1.2 years (median: 5.3 years). All patients had a history of diabetes in at least one of their 1st or 2nd-degree relatives. Anthropometric measurements and demographic characteristics of the patients at the time of diagnosis are given in Table 1.

Biochemical properties

At the time of diagnosis, mean fasting blood glucose was 137.0±52.4 mg/dl, insulin 6.1±2.8 mU/L, c-peptide 1.4±0.6 ng/mL, triglyceride 106.1±42.3 mg/dL, and cholesterol 154.0±19.0mg/dL. While HbA1c was 6.3±0.4 at the time of diagnosis, it was 6.2±0.4 at the end of the mean 5-year treatment follow-up, and there was no statistical difference between these measurements ($p = 0.073$) (Table 2). The glucose and lipid profiles at the time of diagnosis are shown in Table 2. Diabetes-related autoantibodies (anti-insulin, anti-islet, anti-GAD antibodies) in all of our patients were negative at the time of diagnosis and during the follow-up.

Molecular findings

As a result of the analysis, homozygous c.565A>G (p.Ile189Val) changes were detected in 4 patients. In addition, heterozygous c.565A>G (p.Ile189Val) changes in 3 patients, c.667G>A (p.Gly223Ser) and c.1178T>C (p.Met393Thr) changes in 2, and c.704T>C (p.Met235Thr) and c.1195G>T (p.Glu399Ter) changes in 1 patient were detected. The data containing the evaluations regarding the detected variants' pathogenicity are shown in Table 3.

Table 1. Anthropometric measurements and demographic characteristics of the patients at the time of diagnosis.

F	P	Birth weight (g)	Gestational age (weeks)	Age (years)	Boy SDS	Pubertal status	Height SDS	Weight SDS	BMI SDS	GDM	CM
F1	P1 (M)	3000	40	8.1	-0.50	Prepubertal	-0.39	-0.90	-0.90	-	-
	P2 (F)	2600	39	2.5	-0.88	Prepubertal	-1.07	-0.77	-0.77	-	-
F2	P3 (M)	3000	40	7.6	-1.23	Prepubertal	0.12	0.72	0.72	+	+
	P4 (M)	2350	39	13.2	-0.65	Pubertal	-0.34	0.02	0.02	+	+
F3	P5 (F)	3000	40	6.8	1.28	Prepubertal	-0.02	-1.01	-1.01	-	-
F4	P6 (F)	3100	41	11.1	0.31	Prepubertal	-0.44	-0.78	-0.78	-	-
F5	P7 (F)	3200	40	16.9	0.77	Pubertal	-2.00	-1.90	-1.90	+	-
F6	P8 (F)	3000	40	16.8	0.23	Pubertal	1.88	1.80	1.80	-	+
F7	P9 (M)	2900	39	12.2	-0.57	Prepubertal	-1.47	-1.56	-1,56	-	-
F8	P10 (F)	2800	38	10.6	0.15	Prepubertal	1.51	1.76	1,76	+	-
F9	P11 (M)	3400	40	7.5	-0.65	Prepubertal	-0.34	-0.39	-0.39	-	-
F10	P12 (F)	3000	40	11.0	-0.31	Prepubertal	1.22	1.66	1.66	-	-
F11	P13 (M)	2900	39	13.3	-0.36	Pubertal	-1.11	-1.26	-1.26	-	+

F, Family; P, Patient; M, Male; F, Female; BMI, body mass index; SDS, standard deviation score; GDM, gestational diabetes mellitus; CM, consanguineous marriage.

Table 2. Biochemical values at diagnosis, treatment and last measured serum HbA1c levels.

F	P	Glukoz (mg/dL)	Insulin (IU/mL)	c-peptid	First HbA1c	TC (mg/dL)	LDL –C (mg/dL)	HDL –C (mg/dL)	TG (mg/dL)	Treatment	Last HbA1c
F1	P1 (M)	108	2.96	1.14	5.8	135	65	43	136	Diet, exercise	5.6
	P2 (F)	303	3.2	0.7	6.5	160	91	58	52	Diet, exercise, metformin	6.3
F2	P3 (M)	129	1.9	0.58	5.8	145	70	52	115	Diet, exercise	6.2
	P4 (M)	132	5.0	1.5	6.6	121	36	44	198	Diet, exercise	6.5
F3	P5 (F)	112	5.8	2.3	5.7	156	8	60	48	Diet, exercise	5.7
F4	P6 (F)	126	6.5	1.9	6.8	146	100	40	94	Diet, exercise	6.5
F5	P7 (F)	114	8.4	1.8	5.9	154	95	43	79	Diet, exercise	5.9
F6	P8 (F)	129	8.14	2.3	6.2	113	59	36	85	Diet, exercise	6.0
F7	P9 (M)	111	7.8	0.8	6.8	152	87	46	98	Diet, exercise	6.5
F8	P10 (F)	126	10.3	2.03	6.7	131	67	36	144	Diet, exercise, metformin	6.5
F9	P11 (M)	113	2.27	0.93	6.5	217	132	54	150	Diet, exercise	6.5
F10	P12 (F)	118	8.2	1.8	6.2	197	122	53	107	Diet, exercise	6.2
F11	P13 (M)	168	9.4	1.3	6.9	176	116	44	74	Diet, exercise, metformin	7.1

F, Family; P, Patient; M, Male; F, Female; HbA1c, glycated hemoglobin; TG, triglyceride; HDL, highdensity lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

Discussion

GCK-MODY and HNF1A-MODY are the most common MODY subtypes. Since it causes asymptomatic hyperglycemia, its frequency may vary according to the health policies of societies, but the actual frequency is unknown. While the common monogenic type of diabetes is MODY-3 in the United Kingdom, Netherlands, and Denmark, the dominant MODY form has been reported as MODY-2 in Spain, Italy, France, Germany, the Czech Republic, and Turkey [6,7,9]. In a study, the prevalence of GCK MODY was 1.1/1000 [10]. The GCK gene encodes the glucokinase enzyme that converts glucose to glucose-6-phosphate, the first rate-limiting step in glycolysis, and is mostly expressed in pancreatic beta cells and hepatocytes. The GCK enzyme acts as a glucose sensor in beta cells and regulates glucose-dependent insulin secretion depending on intracellular glucose changes. Heterozygous inactivating mutations in the GCK gene cause varying degrees of insensitivity to glucose increase in beta cells, and this insensitivity increases the glucose-dependent insulin release threshold, resulting in a fasting glucose increase [11].

When the history of the patients was examined, the mothers of four cases were diagnosed with gestational diabetes mellitus (GDM). Of the cases, 11 were diagnosed because of the incidental elevation in blood glucose values during routine blood analysis and 2 cases due to the diagnosis of MODY-2 diabetes in their siblings. Presentation with gestational diabetes is frequently seen in patients with GCK-MODY diabetes. Since intrauterine growth retardation may occur in pregnancies with GDM diagnosis, it is recommended for patients to be followed carefully during pregnancy, and insulin therapy should be intervened when necessary [12]. Only 1 of our cases with maternal GDM was small for gestational age (SGA) and term. All other cases were born at term and appropriate for gestational

Table 3. Clinical data of patients and pathogenicity information of detected GCK variants.

F	P	Transcript No	Exon	cDNA	Aminoacid	Zigosite	Mutation Taster	Provean	SIFT	ACMG classification	ACMG Pathogenicity Criteria
F1	P1 (M)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HT	D	D	N	LP	PM1,PM2,PP2,PP3
	P2 (F)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HO	D	D	N	LP	PM1,PM2,PP2,PP3
F2	P3 (M)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HO	D	D	N	LP	PM1,PM2,PP2,PP3
	P4 (M)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HO	D	D	N	LP	PM1,PM2,PP2,PP3
F3	P5 (F)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HT	D	D	N	LP	PM1,PM2,PP2,PP3
F4	P6 (F)	NM_001354800.1	7	c.704T>C	pMet235Thr	HT	D	D	D	LP	PM1,PM2,PP2,PP3
F5	P7 (F)	NM_001354800.1	9	c.704T>C	pMet393Thr	HT	D	D	D	LP	PM1,PM2,PM5,PP2,PP3,PP5
F6	P8 (F)	NM_001354800.1	6	c.667G>A	p.Gly223Ser	HT	D	D	D	LP	PM1,PM2,PP2,PP3,PP5
F7	P9 (M)	NM_001354800.1	9	c.1178T>C	pMet393Thr	HT	D	D	D	LP	PS1,PM1,PM2,PP2,PP3,PP5
F8	P10 (F)	NM_001354800.1	6	c.667G>A	p.Gly223Ser	HT	D	D	D	LP	PM1,PM2,PP2,PP3,PP5
F9	P11 (M)	NM_001354800.1	9	c.1195G>T	pGlu399Ter	HT	D	-	D	P	PS1,PM1,PM2,PP2,PP3,PP5
F10	P12 (F)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HT	D	N	B	LP	PVS1,PM2,PP3
F11	P13 (M)	NM_001354800.1	5	c.565A>G	p.Ile189Val	HO	D	N	B	LP	PM1,PM2,PP2,PP3

F, Family; P, Patient; M, Male; F, Female; BMI, body mass index; SDS, standard deviation score; GDM, gestational diabetes mellitus; CM, consanguineous marriage.

age (AGA).

The GCK gene shows full penetrance, and a clinic with mild hyperglycemia occurs in affected family members. It is possible to be diagnosed incidentally during routine laboratory examinations for any reason or while evaluating glucose intolerance during pregnancy. Glucose increase (<90 mg/dL) at the 120th minute in the OGTT performed in these patients is low [13]. They are usually diagnosed with mild fasting hyperglycemia detected during screenings. Fasting hyperglycemia is present from birth, but a slight clinical progression can be observed with age. Generally, fasting blood sugars are 100-145 mg/dl, and HbA1C levels are slightly higher than normal (mean 6.5%). Hyperglycemia is not progressive, and HbA1c ranges from 5.6 to 7.3 and does not exceed 8. Since it shows autosomal dominant inheritance, similar findings can be found in the patients' parents. It is stated that individuals with GCK MODY have a low risk of diabetes in terms of long-term micro/macrovascular complications, and individuals can be followed up with diet alone [1,13-16]. It has been shown that 40-50% of children with asymptomatic or incidental hyperglycemia have GCK-MODY [17,18]. It does not require any treatment other than insulin therapy, which can be used to prevent fetal macrosomia in some pregnant women [19,20]. MODY cases can be confused with type 1 diabetes, which occurs after adolescence, or type 2 diabetes, which starts at a young age. If type 1 diabetes is suspected, a differential diagnosis should be made by looking at autoantibodies. In all of our cases, glucose levels were regulated, and there was no need for insulin. There were no signs of insulin resistance in our patients. However, three of our patients used oral antidiabetics (metformin) before the diagnosis of MODY was confirmed and were subsequently discontinued because they did not benefit. Individuals with MODY-2 do not require or even respond to treatment with insulin or oral medications unless they develop type 1 or 2 diabetes [21,22]. Although microvascular and macrovascular complications have been reported in a few cases, it is known that glucokinase heterozygous mutations generally have a good prognosis and can only be followed with a diabetic diet [23,24]. No macrovascular and microvascular complications were observed in our patients at the time of diagnosis and after a mean follow-up of 5 years.

GCK mutations account for 30-60% of all MODYs, and the highest prevalence are reported from Southern European countries [25]. More than 800 mutations have been identified in the GCK gene; furthermore, point mutations account for 71%, splicing and regulatory region mutations for 9%, and deletion/insertion mutations for 20% of all mutations [4]. The Sanger sequencing method makes it possible to detect base substitutions and small indels (insertions or deletions) in the coding and regulatory regions, but it is unable to detect large deletions. The most widely used method today for investigating these mutations is the multiplex ligation-dependent probe amplification (MLPA) method. It should also be kept in mind that deletion mutations may be present in cases with normal Sanger sequence analysis and clinically thought to be GCK-MODY. In studies on MODY conducted in Turkey, the frequency of GCK mutations varied between 18-64% [26-29]. More accurate data on both the prevalence of GCK-MODY and the genotype-phenotype relationships can be obtained with larger series studies.

One of the most interesting results of our study is that 4 of our cases carrying homozygous mutations in the GCK gene were not diagnosed with neonatal diabetes. Homozygous inactivating mutations of GCK are known to cause permanent neonatal diabetes [3,5,30-32]. However, although rare in the literature, a total of 4 cases of homozygous mutations in this gene, 3 in childhood and 1 in adulthood, have been reported to present with mild hyperglycemia [30-32]. They suggested that protein stability plays a role in determining the clinical severity of GCK mutations [30-32]. It has been emphasized that cases carrying some homozygous GCK mutations may rarely present at a later period. The results of our study support this idea. The fact that we did not perform any functional study for these mutations in our study is an important shortcoming of this study.

The fact that incidental and non-progressive mild hyper-

glycemia is an important finding in the diagnosis and the homogeneity of the clinical phenotype among cases makes it easier to identify patients with the possibility of GCK-MODY. Generally, a healthy diet and lifestyle recommendations are sufficient to achieve metabolic control that does not require any treatment. It also showed that diabetes due to homozygous mutations in the GCK gene can occur in childhood, albeit rarely. With the molecular diagnosis of GCK-MODY, the patient's treatment plan, follow-up, and long-term prognosis will be predicted more accurately.

Ethics approval

The study was approved by the Malatya Training and Research Hospital Ethics Committee (23536505-000-4044).

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