case report

Clinical follow-up of two Brazilian subjects with glucokinase-MODY (MODY2) with description of a novel mutation

Seguimento clínico de dois pacientes brasileiros com MODY-glicoquinase (MODY2) e descrição de uma nova mutação

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SUMMARY

Mutations in the glucokinase gene (*GCK*) account for many cases of monogenic diabetes featuring maturity-onset diabetes of the young type 2 (MODY2). The clinical pattern of this form of hyperglycemia is rather stable, with a slight elevation in blood glucose, which is usually not progressive. Patients rarely require pharmacological interventions and microvascular complications related to diabetes are unusual. We describe the clinical follow-up of two cases of MODY2 with two different mutations in *GCK* gene, one in exon 7, p.Glu265Lys (c.793 G> A), which has been previously described, and a novel one, in exon 2, p.Ser69Stop (c. 206C> G). The clinical course of both cases shows similarity in metabolic control of this form of diabetes over the years. Arq Bras Endocrinol Metab. 2012;56(8):490-5

SUMÁRIO

Mutações no gene da glicoquinase (*GCK*) são determinantes de uma forma de diabetes monogênico denominada de MODY2 (*maturity-onset diabetes of the young*, tipo 2). O padrão clínico dessa forma de distúrbio glicêmico é bastante estável, com hiperglicemia leve, geralmente não progressiva. Intervenções farmacológicas raramente são necessárias e complicações crônicas secundárias ao diabetes são infrequentes. Descrevemos o acompanhamento clínico de dois casos de MODY2 com duas mutações diferentes, uma no éxon 7, p.Glu265Lys (c.793 G>A) já descrita anteriormente, e outra inédita no éxon 2 p.Ser69Stop (c. 206C>G). A evolução clínica de ambos os casos demonstra uma semelhança no padrão metabólico dessa forma de diabetes ao longo dos anos. Arq Bras Endocrinol Metab. 2012;56(8):490-5

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INTRODUCTION

Maturity onset diabetes of the young (MODY) refers to a group of clinically heterogeneous hereditary forms of diabetes that are defined at the molecular genetic level by mutations in different genes. All subtypes show beta-cell dysfunction associated with defects in insulin secretion, usually with young-onset of diabetes (childhood, adolescence, or young adults), autosomal dominant inheritance (presence of three generations of the same affected lineage) with variable clinical features depending on the mutated gene (1-3). MODY is one of the monogenic forms of diabetes to be distinguished from the polygenic types of diabetes, es-pecially type 1 and type 2, which involve more complex combinations of genetic and environmental factors. At least seven forms of MODY have been described by molecular genetic studies of diabetes, and are related to mutations in Glucokinase (*GCK*), *HNF1A*, *HNF4A*, *HNF1B*, *NEUROD1*, *PDX1*, and *INS* genes, with different clinical presentations. Identification of a MODY mutation is important for correct diagnosis, appropriate genetic counseling, evaluation of prognosis, and selection of the best treatment (4,5). MODY is rare, with an estimated prevalence between 0.3% and 2.4% of the diabetes cases, although these figures are considered underestimations; mutations in *HNF1A* and

GCK genes account for approximately 70% of cases in all populations studied (3,6), including in Brazil (7-9).

Glucokinase (*GCK*) belongs to the hexokinase family of enzymes, and catalyses the conversion of glucose to glucose-6-phosphate in the first reaction of the glycolytic pathway (10). *GCK* plays a major role in the regulation of insulin release and has been termed the glucose sensor of pancreatic beta-cells because of its ability to alter glucose phosphorylation rates over a range of physiological glucose concentrations (11). The key regulatory role of *GCK* in the pancreatic beta-cells explains why mutations in this gene can result in both hyper- and hypoglycemia. For instance, gain-of-function heterozygous *GCK* mutations have been identified in patients with congenital hyperinsulinism (CHI) characterized by inappropriate oversecretion of insulin despite hypoglycemia (12). Meanwhile, a total of twelve *GCK* loss-of-function mutations have been reported in permanent neonatal *diabetes mellitus* (PNDM).

The clinical features that suggest the diagnosis of MODY2 are: a) persistent and stable fasting hyperglycemia over a period of months or years; b) glycated hemoglobin (HbA1c) frequently just below or just above the upper limit of normal; c) small blood glucose increment (less than 60 mg/dL) after an oral glucose overload test (2hr glucose – fasting glucose); d) parents may have diabetes or at least one parent may have mildly raised fasting blood glucose; it is important to test fasting glucose in apparently unaffected parents (13,14). Existence of heterogeneity in the clinical phenotype of patients carrying *GCK* mutations has already been described, including uncommon presentations such as overt neonatal hyperglycemia, marked postprandial hyperglycemia, glucosuria, and even ketoacidosis (15-17). However, overall, the pattern of mild hyperglycemia is usually quite stable in most patients. Microvascular complications are very unusual in *GCK*-MODY, and pharmacological treatment is rarely needed, since most cases are managed by diet alone (5,13,18,19).

MODY diagnosis is defined by molecular genetics and predicts disease prognosis, besides identifying risk of diabetes in family members. However, genetic testing is expensive, so careful consideration is required when determining which patients should be tested (6).

The aim of this study was to report the clinical follow-up of two Brazilian patients with heterozygous *GCK* mutations, since the natural course of MODY2 is still unknown within our population. We also described a new mutation in *GCK* gene.

PATIENTS AND METHODS

Clinical and laboratory data were collected from each patient's records. The following biochemical parameters were measured on fasting blood samples: plasma glucose (FPG) by enzymatic method; cholesterol and triglycerides by colorimetric enzymatic method; HbA1c by high performance liquid chromatography (HPLC); serum fasting insulin, serum fasting C-peptide, anti-glutamic acid decarboxylase (GADA), anti-islet cell (ICA512) and anti-insulin (IAA) by radioimmunoassay. Oral glucose tolerance test (OGTT) was evaluated in fasting blood samples, and 2 hours after an oral glucose dose of 0.75 g/kg body weight (maximum 75 g). Homeostasis model assessment (HOMA) indexes of beta-cell function (%B) and insulin sensitivity (%S) were computed with the HOMA Calculator – version 2.2 (20).

Genetic testing of case 1 was performed in Exeter, UK, and of case 2, in Unifesp, Brazil. Genomic DNA was extracted from peripheral blood leukocytes by standard procedures; exons 1A-10 and exon-intron boundaries of the *GCK* gene were screened for mutation by direct sequencing using Big Dye Terminator on ABI PRISM 3131XL Genetic Analyzer (Applied Biosystems, UK). Polymerase chain reaction (PCR) primers were supplied on demand.

Parents of both subjects gave their written informed consent for genetic analysis and disclosure of the results. The research was approved by the Ethics Committee of Escola Paulista de Medicina, Unifesp.

Patient 1

The index patient was a boy, the only child to non-consanguineous parents, born at term with a birth weight of 2.900 g (SDS -1.08) and length of 48 cm (SDS -0.74), whose growth and neurological development were normal. At 11 years of age, during laboratory tests for the investigation of tonsillitis, he showed fasting blood glucose level of 125 mg/dL. The test was repeated a few days later and resulted in 123 mg/dL. OGTT was performed with the following values: fasting, 112 mg/dL and 2 h post-load: 151 mg/dL, consistent with the American Diabetes Association (ADA) criteria for impaired fasting glucose and impaired glucose tolerance (pre-diabetes) (21). His pubertal development was normal for age, and no other health problems were disclosed in physical examination. In his family history, the father reported impaired fasting blood glucose level of 110 mg/dL, which could not be confirmed, and cases of diabetes were denied.

Laboratory investigation demonstrated negative results for anti-glutamic acid decarboxylase (GADA), anti-islet cell (ICA512) and anti-insulin (IAA) self-antibodies. Fasting C-peptide levels showed good pancreatic reserve (1.4 ng/mL; reference value: 1.1-4.4 ng/mL), and HbA1C was 6.1% (reference value: 4.8-5.9%). Based on his clinical presentation, the hypothesis of MODY2 was formed. Sequencing of the *GCK* gene identified a mutation in exon 7, p.Glu265Lys (c.793 G>A). The patient was advised to perform regular physical activity for weight maintenance. Clinical follow-up demonstrated stable fasting blood glucose, and HbA1C levels around 6.3% (ranging from 5.9% to 6.8%; HPLC) in a period of more than 9 years. He had normal pubertal development with no worsening of glycemic control (Table 1). No medication was prescribed throughout this period. The patient remained very active, always practicing regular physical activity, maintaining normal weight and body mass index (BMI). His parents did not want to perform genetic tests.

Patient 2

The proband was a girl, the second child of a non-consanguineous parents, born at 38 weeks of gestation, with a birth weight of 2.740 g (SDS -1.29), length of 46 cm (SDS -1.44). The mother was diagnosed with hypothyroidism and gestational diabetes, and treated with levothyroxine and insulin; she remained diabetic after delivery, with irregular use of metformin. Her father was obese and the maternal great-grandmother, grandmother, and grandfather had diabetes treated with sulphonylurea. The postnatal course was uncomplicated but growth retardation was observed during the first 6 months of life, and mild hyperglycemia was detected in the laboratory work-up (Table 2). At 18 months of age, type 1 diabetes-associated self-antibodies (ICA512, GADA, IAA) were negative, C-peptide level was 0.7 ng/mL, HbA1c was 6.6% and fasting blood glucose was 136 mg/dL. The hypothesis of MODY2 was formed, and the family was advised about the importance of a healthy lifestyle with balanced diet and regular physical activity for better prognosis. However, after 2 years of age, she was started on cafeteria food and her weight gain was progressively greater, despite her growth rate remaining stable, in the familial growth pattern (SDS -1.74) (Figure 1). Some episodes of postprandial hyperglycemia (197; 180; 201 mg/dL) were detected by self-monitoring of blood glucose, without glucosuria. Serial OGTTs were performed and the results were consistent with the ADA criteria for impaired fasting glucose and impaired glucose tolerance (pre-diabetes) in most occasions (21) (Table 2). During her clinical follow-up throughout the next 8 years, she maintained fasting blood glucose between 117-132 mg/dL and HbA1c between 6.6%-6.8% (Table 2). Recently, she started pubertal development (Tanner B1P2) at the age of 10 years and 3 months, with bone age of 11 years. Sequencing of the *GCK* has recently identified a nonsense mutation p.Ser69Stop (c. 206C>G) in the proband and her mother. Her father, without history of diabetes, showed no mutation.

Table 1. Clinical follow-up of patient 1 from 13 to 21 years old with biochemical analysis and fundoscopy

Age (years-months)	13y	14y-9m	15y-9m	16y	16y-6m	17y	19y-1m	20y	21y-6m
Weight (kg)	63		70						70
Height (cm)	182		186						187
BMI (kg/m²)	19		20.3						20
Fasting blood glucose (75-99 mg/dL)*	121	116	121	121	134	120	134	126	115
Fasting plasma insulin (2-25 µUI/mL)*		9.1							5.5
HOMA$_{IR}$/HOMA$_S$ (%)		1.3/79.8							0.8/ 131.4
HOMA$_{beta}$ (%)		64.7							46.5
HbA1c (4.8-5.9%)	6.3	6.1	6.6	6.8	6.5	6.3	6.6	6.5	5.9
C-peptide (1.1-4.4 ng/mL)*	1.3	1.03		0.98					1.5
Cholesterol (< 170 mg/dL)*				167					
HDL cholesterol (≥ 35 mg/dL)*						33			
LDL cholesterol (< 110 mg/dL)*						68			
Triglycerides (< 130 mg/dL)*				70	66	66			
Microalbuminuria (< 20 µg/min)*				Normal			Normal		Normal
Fundoscopy				Normal			Normal		Normal

* Reference values.

Table 2. Clinical follow-up of patient 2 from birth to 10 years old with biochemical analysis and fundoscopy

| Age (years-months)	Birth	8m	1y	4y-10m	5y-11m	6y-6m	7y-9m	8y-6m	9y-6m	10y-6m
Weight (kg)	2.740	7.040	8.700	21.5	25	29.3	32	34.6	38	46
SDS	-1.29	-1.47	-0.99	+1.24	+1.26	+1.6	+1.27	+1.16	+0.96	+1.33
Height (cm) SDS	46	62	68	101	109	112.5	117.5	120.5	124.5	129.5
	-1.44	-2.57	-2.13	-1.26	-1.08	-1.14	-1.59	-1.73	-1.78	-1.5
BMI-SDS				+2.31	+2.16	+2.15	+2.13	+2.02	+2.01	+2.18
Fasting blood glucose (75-99 mg/dL)*		108	133	132	117	131	126	122	126	126
120-min blood glucose (<140 mg/dL)*			148	127						155
Fasting plasma insulin (2-25 µUI/mL)*				7.55	3.49	11.1	6.97			17.0
120-min plasma insulin (µUI/mL)*				15.16	14.93					67.0
HOMA$_{IR}$ /HOMA$_S$ (%)				1.1 /93.3	0.5/205.5	1.6 /64.0	1.0/101.9			2.3/42.6
HOMA$_{beta}$ (%)				44.2	33.0	58.8	45.8			85.7
HbA1c (4.8-5.9%)			6.6	6.6	6.8	6.8	6.6	6.8	6.7	6.9
C-peptide (1.1-4.4 ng/mL)*				1.97				1.46		
HDL cholesterol (≥ 40 mg/dL)*								59	47	43
LDL cholesterol (<110 mg/dL)*								97	82	11
Triglycerides (< 100 mg/dL)*								41	36	48
IGF1 (20-200 ng/mL)*			49							
Microalbuminuria (< 20 µg/min)						4		4		4
Fundoscopy								Normal	Normal	

* Reference values.
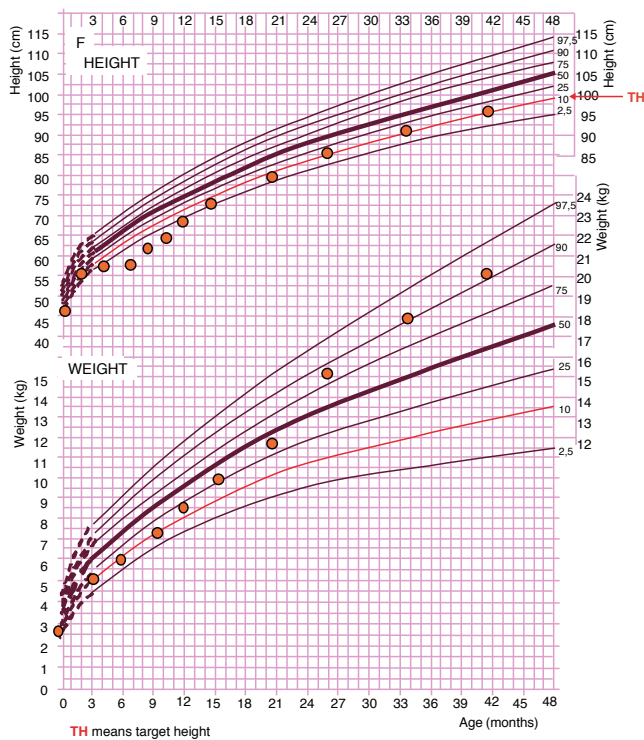
Figure 1. Growth chart of a patient with MODY2.

DISCUSSION

We describe here the clinical follow-up of two *GCK*-MODY pediatric patients whose metabolic control was uneventful without diabetes-related complications. Molecular analysis demonstrated a missense mutation p.Glu265Lys (c.793 G>A) in patient 1, which has already been described in Italian, Spanish, and British populations (22-24). Previous functional studies demonstrated that this mutation strongly affects protein stability (25). In patient 2, a novel nonsense mutation p.Ser69Stop (c. 206C>G) in exon 2 was identified in the patient and her mother, thus demonstrating the co-segregation of this mutation and *diabetes mellitus* phenotype.

A total of 620 *GCK* mutations have been identified in 1,441 families with PNDM, MODY, or CHI. Mutations are distributed throughout the gene and no common mutations or "hot spots" have been found (24). All MODY2 cases are made up of heterozygous for nonsense, missense, or frameshift mutations and result in a deficiency of *GCK* activity (26-29). More than 50 mutations were functionally characterized, and most of

them alter the kinetics of the enzyme. In other mutations where kinetics was normal, the mutational mechanism may be related to the effect on enzyme stability (as in our case 1), or binding to regulatory molecules (24). There is no clear association between phenotype (i.e., insulin secretion) and genotype (including type, topography) in *GCK*-MODY patients (30).

In an 11-year period of follow-up, it was observed that glucose tolerance of MODY2 adult subjects may remain stable for many years, probably because of the stability of the glucokinase-related beta-cell defect. However, if or when insulin resistance develops, the beta-cell defect may impair the increase in insulin secretion, and may result in deterioration of glucose tolerance (31). Of note, our patient 2 became obese and there was a noticeable variation in insulin sensitivity measured by $HOMA_{IR}/HOMA_S$. However, the index of insulin secretion $HOMA_{beta}$ was persistently less than 100%, even when $HOMA_{IR}/HOMA_S$ was 2.3/42.6%, suggesting failure in insulin secretion (Table 2). In both cases, but particularly in case 1, the stability of C-peptide plasma levels all over this period suggests stability of pancreatic beta-cell reserve in MODY2 (Table 1), in contrast with the findings commonly observed in patients with DM2, and especially with DM1 (32).

It has been recently demonstrated in a cohort of healthy children aged 5-14 years who were enrolled in the Early Bird Diabetes study, that insulin resistance starts to rise in mid-childhood, some years before puberty, mostly independent of rising adiposity and insulin-simile growth factor-1 (IGF-1) (33). The condition of Patient 1 remained under control throughout his pubertal development, reinforcing the concept that hyperglycemia in MODY2 remains stable over time. Patient 2 has only recently initiated pubarche.

Another interesting aspect is the existence of a possible relationship between *GCK* mutation and growth retardation. Failure to thrive motivated the reference of Patient 2 to further investigation. Intrauterine growth retardation and reduced birth weight are clinical manifestations frequently described in infants with permanent neonatal *diabetes mellitus* due to mutations in *KCNJ11*, *ABCC8* (34), *INS* (35,36), *PDX1* (37) genes, and in homozygous *GCK* mutations in children within the first few days of life (26,29), as a reflection of insulin deficiency *in utero*. Studies with *GCK*-MODY pedigrees demonstrated that *GCK*-MODY newborns are lighter than their unaffected siblings, independent of the parental origin of the mutation (38-40). Hat-

tersley and cols. (41) analyzed the impact caused by a heterozygous mutation in the *GCK* gene in fetal growth and birth weight of 58 children from 10 extended *GCK* pedigrees, and observed that the inheritance of a *GCK* mutation by the fetus resulted in mean birth weight reduction of 533 g (p = 0.002). Length at birth was also reported in 26 children, and the presence of a fetal *GCK* mutation significantly reduced length (50.3 ± 5.3 *vs.* 55.5 ± 2.3 cm; p = 0.009). These studies brought evidence that birth weight is also determined by fetal genotype. Velho and cols. demonstrated that a large proportion of babies show early postnatal catch-up after birth, as observed in our case 2. Also, they found that neither maternal nor fetal mutations alter adult height or weight of the offspring (42).

In conclusion, we described two Brazilian patients carrying mutations in the *GCK* gene, whose 9-year clinical follow-up confirmed the stability of metabolic control and absence of vascular complications without antidiabetic medications. We also report a novel nonsense mutation p.Ser69Stop (c. 206C>G) associated with the MODY2 phenotype. This case report reinforces the importance of genetic diagnosis of monogenic forms of diabetes in order to establish prognosis and appropriate treatment intervention.

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