

Maturity onset diabetes of young type 2 due to a novel *de novo* GKC mutation

Diabetes monogênica tipo MODY com início na juventude causado por uma mutação GKC de novo não descrita anteriormente

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SUMMARY

Maturity Onset Diabetes of Young (MODY) is a heterogeneous group of monogenic disorders that result in β -cell dysfunction, with an estimated prevalence of 1%-2% in industrialized countries. MODY generally occurs in non-obese patients with negative autoantibodies presenting with mild to moderate hyperglycemia. The clinical features of the patients are heterogeneous, depending on the different genetic subtypes. We pretend to report a case of MODY type 2 caused by a novel *de novo* CGK mutation, highlighting the importance of the differential diagnosis in pediatric diabetes. A 13-year-old, healthy and non-obese girl was admitted for investigation of recurrent hyperglycemia episodes. She presented with persistent high levels of fasting blood glycemia (> 11.1 mmol/L) and had no familial history of diabetes. The blood glucose profile revealed an impaired fasting glucose of 124 mg/dL (6,9 mmol/L) with a normal oral glucose tolerance test. Fasting insulinemia was 15 mg/dL (90.1 pmol/L), HOMA-IR was 3.9 and hemoglobin A1c was 7.1%. Pancreatic autoantibodies were negative. Genetic testing identified a novel missense heterozygous mutation in exon 5 of *GCK* gene c.509G $>$ T (p.Gly170Val), not present on the parents. This result established the diagnosis of MODY type 2. Clinical identification of patients with MODY remains a diagnostic challenge, especially when familial history is absent. Molecular diagnosis is very important for establishing an individualized treatment and providing a long term prognosis for each type of MODY. *Arq Bras Endocrinol Metab.* 2014;58(7):772-5

SUMÁRIO

O diabetes da maturidade com início na juventude (MODY) é um grupo heterogêneo de doenças monogênicas que resultam em disfunção das células β , com uma prevalência estimada de 1-2% nos países industrializados. O MODY geralmente ocorre em pacientes não obesos, negativos para autoanticorpos e que apresentam hiperglicemia de leve a moderada. As características clínicas dos pacientes são heterogêneas e dependem do subtipo genético. Pretende-se relatar um caso de MODY tipo 2 causado por uma mutação GKC *de novo* não descrita anteriormente, demonstrando a importância do diagnóstico diferencial no diabetes pediátrico. Uma menina de 13 anos de idade, saudável e não obesa, foi admitida em um hospital para investigação de episódios recorrentes de hiperglicemia. Ela apresentava níveis altos e persistentes de glicemia de jejum ($> 11,1$ mmol/L) e não havia histórico familiar de diabetes. O perfil glicêmico sanguíneo revelou glicose de jejum de 124 mg/dL (6,9 mmol/L), com resultados normais no teste oral de tolerância à glicose. O resultado da insulinemia de jejum foi 15 mg/dL (90,1 pmol/L), do HOMA-IR foi 3,9 e da hemoglobina A1c foi de 7,1%. Os autoanticorpos pancreáticos foram negativos. A análise genética identificou uma nova mutação heterozigota missense no éxon 5 do gene *GCK* c.509G $>$ T (p.Gly170Val), não encontrada nos pais. Esse resultado estabeleceu o diagnóstico de MODY tipo 2. A identificação clínica dos pacientes com MODY permanece um desafio diagnóstico, especialmente quando não existe um histórico familiar. O diagnóstico molecular é muito importante para se estabelecer um tratamento individualizado e oferecer um prognóstico de longo prazo para cada tipo de MODY. *Arq Bras Endocrinol Metab.* 2014;58(7):772-5

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Received on Nov/27/2013
Accepted on Aug/18/2014

DOI: 10.1590/0004-2730000003147

INTRODUCTION

Maturity onset diabetes of the young (MODY) is a heterogeneous group of monogenic disorders that result in β -cell dysfunction. It has an estimated prevalence of just 1%-2% of all diabetes in industrialized countries, however this prevalence is probably underestimated since large population screening studies have not been performed (1).

The first clinical case reports were described in the 1970s, as a familial form of noninsulin-dependent diabetes with autosomal dominant inheritance, presenting before the age of 25 years (2,3). The molecular genetic basis of MODY was subsequently recognized in the 1990s (4-8) and diagnostic genetic testing for common subtypes followed rapidly. To date, 13 different genetic etiologies associated with different clinical features have been identified (9-11). The clinical features of patients with MODY are heterogeneous, depending on the different genetic subtypes.

There may be an overlap between MODY's clinical presentation and type 1 and type 2 diabetes, but an accurate diagnosis must be achieved in order to establish the proper management and treatment.

The typical clinical picture in MODY, as well as the prognosis and specific treatment response, are extremely dependent on the genetic etiology. Mutations in the genes encoding the enzyme glucokinase (*GCK*) and the nuclear transcription factors hepatocyte nuclear factor 1 α (*HNF1A*) and hepatocyte nuclear factor 4 α (*HNF4A*) are the most common causes of MODY. *GCK* mutations are more commonly diagnosed in countries where glucose screening in asymptomatic people is a routine procedure (such as Germany, France, Spain and Italy), whereas *HNF1A*-MODY is more commonly diagnosed where routine glucose screening is seldom done (12,13). There also some reported MODY cases in Brazilian literature (14-18).

CASE REPORT

We report the case of a 13-year-old girl admitted to Diabetes Consultation for investigation of recurrent hyperglycemia episodes.

Her family background was unremarkable, with no familial history of diabetes.

She was the second child of non-consanguineous parents. She had an uneventful full term gestation with a cesarean delivery. Her birth weight was on the 10th percentile. She had no complications in the neonatal

period. She achieved all the developmental milestones. Her past medical history was unremarkable with no known allergies, hospitalizations or serious illnesses.

One year before being admitted in our Consultation, she performed routine blood screening that showed hyperglycemia with a fasting blood glycemia of 124 mg/dL (7,1 mmol/L).

During that year, she presented with three episodes of postprandial blurred vision and dizziness. In routine evaluation she had persistently high levels of fasting blood glycemia, all superior to 200 mg/dL (11,1 mmol/L). She had no history of polyphagia, polyuria, polydipsia or weight loss.

The physical examination was unremarkable with normal vital parameters and a body mass index of 18,2 kg/m².

A blood glucose profile was obtained, and she was found to have an impaired fasting glucose of 124 mg/dL (6,9 mmol/L) and a normal oral glucose tolerance test with a glucose increment of only 3 mg/dL (0,2 mmol/L) after 120 minutes of glucose ingestion. Fasting insulinemia was 15 mg/dL (90,1 pmol/L), HOMA-IR was 3.9 and hemoglobin A1c was slightly elevated with a level of 7,1%. Pancreatic auto antibodies were negative.

Even though she had a negative familial history of diabetes, acute onset of Maturity Onset Diabetes of Young (MODY) was suspected and genetic testing was performed. Genomic DNA of the patient was isolated and PCR amplification of the pancreas-specific exon 1a as well as of exons 2-10 of the *GCK* gene was performed. Sequencing of the PCR products identified a novel missense heterozygous mutation encoded by exon 5 at position c.509G > T resulting in the amino-acid change p.Gly170Val.

Genetic study was also performed to the patient's parents, who were asymptomatic and showed no mutation on *GCK* gene.

This novel mutation on *GCK* gene, associated with a typical MODY type 2 clinical picture, in the absence of the mutation on both parents, suggests we are in presence of a MODY type 2 caused by a novel *de novo* mutation.

Based on the diagnosis of MODY type 2, the proposed treatment was only a lifestyle modification with regular physical activity and a well balanced diet. The patient has been clinically stable and the last laboratory evaluation showed a fasting glycemia of 112 mg/dL (6,2 mmol/L) with a hemoglobin A1c of 5,7%.

DISCUSSION

MODY diagnosis in pediatric patients may be challenging, especially when establishing the differential diagnosis between monogenic, type 1 and type 2 diabetes.

Being the most frequent type of diabetes in pediatric age, type 1 diabetes can be easily misdiagnosed in children presenting with hyperglycemia due to monogenic diabetes. The fact that monogenic diabetes usually presents with normal insulin and C peptide values, negative pancreatic autoantibodies and rarely presents with ketoacidosis are important features that help distinguish between MODY and type 1 diabetes.

The main differences between monogenic and type 2 diabetes are the fact that monogenic diabetes usually doesn't present with insulin resistance features such as acanthosis nigricans, central obesity, hypertension and dyslipidemia. Generally both monogenic and type 2 diabetes have a marked familial history of diabetes.

In this particular case, as MODY is caused by a *de novo* mutation, the usual familial history is not present leading to diagnostic challenges. It was not possible to test affected relatives, as they were all asymptomatic, in order to investigate co-segregation with *de novo* diabetes/hyperglycaemia.

With this case report we emphasize the need of a high level of clinical suspicion in patients with a clinical typical picture of MODY but without the usual marked familial history.

GCK catalyzes the ATP-dependent phosphorylation of glucose in the first, rate-limiting step of glycolysis in pancreatic β -cell, which enables β -cell and the hepatocyte to respond appropriately to the degree of glycemia (19,20).

To date more than 620 *GCK* gene mutations have been reported in over 1400 patients with *GCK*-MODY (21-23). The mutations are localized over the ten exons of the gene which encode the pancreatic beta cell isoform of glucokinase.

Heterozygous inactivating mutations include missense, nonsense, splicing and small deletions/insertions/duplications variants. Here we report a novel heterozygous missense mutation c.509G > T (p.Gly170Val) on exon 5 of *GCK* gene. To our knowledge this mutation has not been reported before in the literature.

GCK mutations reset the glucose threshold and the insulin secretion becomes up regulated, producing a higher fasting glucose level (24).

Therefore patients demonstrate mild, stable fasting hyperglycemia (99-144 mg/dL; 5.5-8.0 mmol/L) that shows little deterioration with age. They generally are asymptomatic and diagnosis is usually established during routine screening, like in our patient. As there is no impairment in the insulin production, glucose levels rapidly return to normal after an oral glucose load, as described in this patient. Most patients with mutations in the *GCK* have a small increase in plasma glucose (5,4 mg/dL/0,3 mmol/L in 70% of patients) 2 hours after an oral glucose load (25).

In MODY type 2, glycated hemoglobin (HbA1c level) is usually below 8% and there seems to be neither diabetes related microvascular nor macrovascular complications associated (26-28).

Accounting for the lack of long-term complications and the fact that treatment in MODY type 2 seems to have little effect on glycemia and HbA1c (29,30), the general consensus is that the majority of pediatric patients do not require medical treatment (31).

Molecular diagnosis is, therefore, very important for establishing an individualized treatment for each type of MODY and for providing a reliable long term prognosis for individual patients and their relatives.

Disclosure: no potential conflict of interest relevant to this article was reported.

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