Carvalho AL, et al., J Neonatol Clin Pediatr 2023, 10: 112
DOI: 10.24966/NCP-878X/100112

HSOA Journal of Neonatology and Clinical Pediatrics

Case report

Gck-Mody (Mody2) - A Novel Variant on Glucokinase Gene in an Adolescent with Mild Fasting Hyperglycemia

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Abstract

Maturity-Onset Diabetes of the Young (MODY) accounts for 2 to 5% of non-type 1 pediatric diabetes cases and is the second most common form of monogenic diabetes, after MODY3. It is a clinically heterogeneous disorder with autosomal dominant transmission characterized by noninsulin-dependent diabetes diagnosed at a young age and absence of autoantibodies. The diagnosis is made through genetic testing with direct gene sequencing. MODY2 is one of the most common MODY subtypes resulting from variants in the GCK gene. The authors present a case report of a female adolescent with mild fasting hyperglycemia, in which was identified a novel variant on GCK gene, with clinical significance. We intend to highlight the importance of GCK-MODY diagnosis through genetic testing, being crucial to avoid unnecessary treatment and to diagnose other family members.

Keywords: Adolescent; Genetic testing; Monogenic diabetes; MODY

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Citation: Carvalho AL, Gomes MB, Almeida AC, Martins S, Antunes A, et al. (2023) Gck-Mody (Mody2) - A Novel Variant On Glucokinase Gene in an Adolescent with Mild Fasting Hyperglycemia. J Neonatol Clin Pediatr 10: 112.

Received: August 29, 2023; **Accepted:** September 6, 2023; **Published:** September 13, 2023

Introduction

Maturity-Onset Diabetes of the Young (MODY) accounts for 2 to 5% of non-type 1 pediatric diabetes cases. MODY2 and is the second most common form of monogenic diabetes, after MODY 3 [1]. It is a clinically heterogeneous disorder with autosomal dominant transmission characterized by noninsulin-dependent diabetes diagnosed at a young age (before 25 years) and absence of autoantibodies [2]. Many patients are misclassified as having either type 1 Diabetes Mellitus (T1DM) or type 2 Diabetes Mellitus (T2DM). Others are erroneously diagnosed with gestational diabetes after performing the diabetes screening during pregnancy. The diagnosis is made by molecular genetic testing through direct gene sequencing. There are different MODY subtypes according to different genetic mutations. These genetic mutations lead to pancreatic β cells dysfunction, resulting in an impairment in glucose sensing and in insulin secretion. The insulin action can be normal or mildly affected. Variants can occur in different genes: hepatocyte nuclear factor-1-alpha *(HNF1A)* in 52-65% (MODY3), glucokinase (*GCK*) in 15-32% (MODY2), hepatocyte nuclear factor-4-alpha *(HNF4A)* in 10% (MODY-1), and less commonly, insulin promoter factor 1 *(IPF1)* (MODY4), hepatocyte nuclear factor-1-beta *(HNF1B)* (MODY5), neurogenic differentiation factor-1 (also called *NEUROD1* or *BETA2)* (MODY6), among others. Some family members have the genetic defect whitout developing diabetes, being the reason unclear. On the other hand, some patients have the classic MODY phenotype without having an identifiable variant in any of the MODY genes [1,3]. The authors present the case of a female adolescent with a novel *GCK* variant and her phenotypic characterization. The correct classification of this adolescent's diabetes was crucial as it allowed prediction on the disease clinical course, management and pharmacological treatment.

Case Report

A 15-year-old female presented at Emergency Department (ED) after the third episode of lipothymia associated with blurred vision, skin paleness and hypersudoresis. She was the first child from non-consanguineous healthy parents, born full term by cesarean delivery (due to non-progressive labor) with a birth weight of 2840g (0.01 standard deviation score (SDS)). Her body mass index (BMI) was always regular and at the time was 18.5kg/m^2 (-0.98 SDS). A month earlier she was observed in her primary care center due to weight loss of 3kg in 1 month, polyphagia, morning nausea and polydipsia. Laboratorial workup revealed fasting plasma glucose (FPG) of 113mg/dL. Hemoleucogram, kidney function, ionogram, transaminases, thyroid function and C-reactive protein were normal. The study was repeated a month later with FPG 123mg/dL and glycated hemoglobin (HbA1c) 6.7%. As relevant family history, her paternal grandfather was diagnosed with T2DM at 60 year of age and was under treatment with an oral antidiabetic agent. Fasting glucose screening was performed on the patient's parents, with normal results.

Physical examination at the admission in ED was unremarkable. Postprandial glycemia was 148mg/dL, without acidosis or ketonemia (0.1 mg/dL). Laboratory test results showed normal complete blood

count and normal values of albumin, magnesium, phosphate, potassium, sodium, chloro, and calcium. Triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein were also normal. Pancreatic auto-antibodies (anti-islet cell, glutamic acid decarboxylase antibodies, islet antigen 2 antibodies and Zinc Transporter 8 antibodies) were negative. Celiac disease screening was negative and thyroid function was normal, with negative thyroid antibodies. Insulin was 15.8 uUI/ml (reference value: 6-27 uUI/mL) and C-peptide 4.82 ng/mL (reference value: 0.8-6.0 ng/mL). A standard oral glucose tolerance test (OGTT) was performed with a fasting glucose of 103mg/dL and a 2-hour glucose of 124mg/dL. The fasting insulin concentration was 3.2uUI/mL and 24.7uUI/mL after 2 hours. . Molecular genetic NGS testing for MODY was carried out, revealing a likely pathogenic heterozygous variant c.1214C>T(p.(Thr405Ile) in the *GCK* gene. She was managed with dietary care and regular physical exercise, without pharmacologic treatment, followed at a Paediatric Endocrinology Unit. Two years later, the adolescent maintains a mild elevation in fasting glucose (range of 106-124mg/dl), as well as in HbA1c (range of 5.9-6.3%) (Figure 1). No macro or microvascular complications were reported. There are no clinical signs of insulin resistance and insulin and C-peptide levels remain normal.

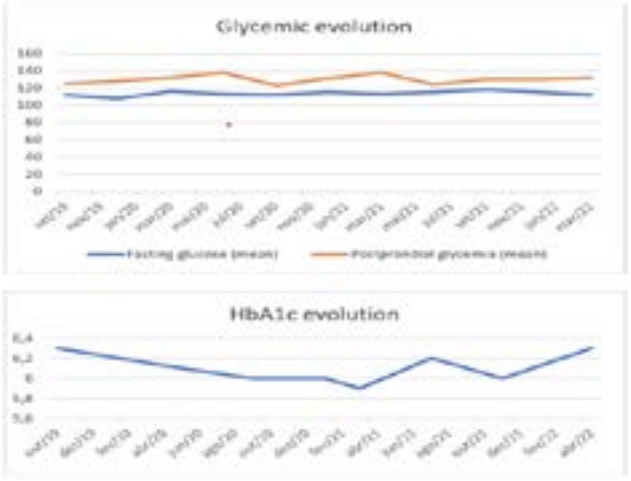

Figure 1: Glycemic and HbA1c Evolution

Discussion

GCK-MODY (formerly called MODY2) is one of the most common MODY subtypes, resulting from variants in the *GCK* gene, located on chromosome 7. *GCK* gene encodes the enzyme glucokinase, with an important regulatory role in glucose metabolism. Commonly referred to as the pancreatic beta cell glucose sensor, glucokinase maintains the glucose homeostasis by modulating glucose-stimulated insulin secretion in response to variations in intracellular glucose concentrations [4]. Heterozygous inactivating *GCK* variants lead to a decreased pancreatic beta cells sensitivity in response to increasing glucose concentrations, subsequently resulting in an increased set point for glucose-stimulated insulin secretion.

GCK was the first gene linked to MODY in French and UK families, in 1992 [5]. Since then, over 600 different *GCK* variants have been described in many populations, the majority identified in Europe [6].

Most of these patients are incidentally discovered during a routine screening and present with mild fasting non-progressive hyperglycemia. Typically, the fasting blood glucose is slightly impaired (98–150 mg/dL) and HbA1c is mildly elevated (5.6 - 7.3%) [7]. Despite lifelong hyperglycemia, patients with *GCK* variants do not have an increased risk of micro and macrovascular complications [8]. Indeed, after two years of follow-up, the adolescent maintains a good metabolic control, without pharmacologic treatment and without macro or microvascular complications.

This condition can be inherited in an autosomal dominant pattern [9], therefore a positive family history for mild diabetes with an early onset should be further investigated. In this case report, no other relatives were found with *GCK*-MODY diagnosis or clinical suspicion.

The diagnosis of diabetes in children and early adulthood with negative pancreatic antibodies and without typical features of T1DM or T2DM and and/or multiple family members with diabetes not characteristic of T1DM or T2DM diabetes should lead to MODY suspicion.

With this case report we intend to register a novel variant on *GCK* gene, with clinical significance. Furthermore, we aim to highlight the importance of MODY diagnosis through genetic testing, being essential to avoid unnecessary treatment and to raise awareness for the subgroup of index cases of MODY. Given the mild phenotype, absence of long-term complications, and inefficacy of unneeded pharmacologic treatment, the general consensus remains that pharmacological treatment is not required except in some cases during pregnancy (as when *GCK* mutation is present in the mother and the fetus doesn´t have the mutation, or it is not inferred) [10, 11].

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