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Short report

A novel heterozygous mutation in the *glucokinase* gene conferring exercise-induced symptomatic hyperglycaemia responsive to sulfonylurea

M.S.E. Ebrahim [a,b], M.L. Lawson [a,*], M.T. Geraghty [c]

[a] *Division of Endocrinology and Metabolism, Children's Hospital of Eastern Ontario, University of Ottawa, 401 Smyth Road, Ottawa, K1H 8L1, Canada*
[b] *Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes, Children's Hospital Cairo University, Cairo University, 11562 Cairo, Egypt*
[c] *Metabolics, Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, K1H 8L1, Canada*

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Abstract

Aim. – To describe the atypical phenotype and genotype of an adolescent girl with symptomatic exercise-induced hyperglycaemia, responsive to sulfonylurea treatment.

Methods. – Chart review, gene sequencing, and blinded continuous glucose monitoring (Medtronic iPro2) were used to characterise the case.

Results. – A novel heterozygous mutation p.Q219x (c.655C>T) in exon 6 of the *glucokinase* gene (NM_000162.3) was confirmed in the patient and father. Initiation of gliclazide 20 mg twice daily was associated with resolution of symptoms and normalization of haemoglobin A1C (5.6%). Blinded continuous glucose monitoring demonstrated significantly less time spent in the hyperglycaemic range (sensor glucose > 8.0 mmol/L) when on twice daily gliclazide versus intermittent or no gliclazide (mean minutes/day with sensor glucose > 8 mmol/L: 53.6 ± 90.0 vs. 307.9 ± 246.6; $P = 0.04$).

Conclusions. – This novel mutation in the *glucokinase* gene led to atypical symptomatic exercise-induced hyperglycaemia that was responsive to low dose sulfonylurea with self-reported additional benefit after reduction of carbohydrate intake. We postulate that her atypical clinical presentation was related to the intense elite-level physical activity combined with carbohydrate loading before exercise.

Keywords: Glucokinase; Heterozygote; MODY2; Sulfonylurea compounds; Exercise

1. Introduction

Inactivating heterozygous mutations in the *glucokinase* gene (GCK) are responsible for 20–50% of the dominantly inherited monogenic diabetes known as GCK-maturity-onset diabetes of the young (GCK-MODY) previously termed MODY2, and also known as Familial Fasting Hyperglycaemia [1]. The more than 600 known GCK mutations have remarkably similar phenotypes: early onset (usually < 25 years of age), persistent mild asymptomatic and non-progressive fasting hyperglycaemia, resulting from a higher set point for insulin release. Typically oral hypoglycaemic agents and insulin have no effect on haemoglobin A1C or glucose levels [2–4]. We describe the atypical phenotype of an adolescent with a novel GCK mutation and symptomatic hyperglycaemia who responded to treatment with oral sulfonylurea.

2. Case report

At the age of 14 years following a self-reported viral illness, a competitive elite-level Caucasian female athlete of Irish descent developed shakiness, tremors and extreme fatigue associated with mild hyperglycaemia. Fasting and postprandial glucometer blood glucoses (BGs) ranged from 122–141 mg/dL [6.8–7.8 mmol/L], with significantly higher levels up to 234 mg/dL [13 mmol/L] noted during and after exercise coinciding with her being most symptomatic. The severity of symptoms was such that they led her to temporarily quit competitive sports. Her appetite had increased over the previous 5 months with unintentional 7.9 pounds [3.6 kilograms] weight loss. There was no polyuria or polydipsia. Past medical history and physical examination were unremarkable. Height was at the

Abbreviations: BG, Blood glucose; GCK, *Glucokinase* gene; GCK-MODY, Glucokinase maturity-onset diabetes of the young; GSIR, Glucose stimulated insulin release; SG, Sensor glucose.

* Corresponding author. Tel.: +1 613 737 2411; fax: +1 613 738 4215.
E-mail address: lawson@cheo.on.ca (M.L. Lawson).

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75th–90th centile (CDC charts) and BMI was 28.7 kg/m^2 (95th centile).

The patient's father was diagnosed with type 2 diabetes at 42 years of age based on fasting venous blood glucose levels of 108 to 117 mg/dL [6–6.5 mmol/L], with subsequent poor metabolic control on metformin, and a myocardial infarction at 44 years of age. The paternal great-grandmother and grandmother were diagnosed with type 2 diabetes at ages 72 and 76 year of age, respectively. The paternal uncle was diagnosed with type 2 diabetes after a myocardial infarction at 43 years of age. Both the father and paternal uncle were reported to have high cholesterol levels. The grandmother and an uncle were managed with metformin; the great-grandmother was initially on insulin but had uncontrolled hypoglycaemia so was controlled solely with diet.

3. Investigations

Investigations at presentation: HbA_{1c} 6.7% (DCA 2000 + analyzer; Siemens Healthcare Diagnostics, Indianapolis, IN, USA; nondiabetic range 4–6.2%); fasting venous BG 122 mg/dL [6.8 mmol/L]; 2-hour BG 140 mg/dL [7.8 mmol/L] after 75-g oral glucose load. Anti-GAD antibodies and islet cell antibodies were negative on two occasions. Fasting insulin and C-peptide were normal at BG level of 140 mg/dL [8.0 mmol/L] (insulin 7.2 uU/mL [52 pmol/L] {normal 1.8–22 uU/mL}, C-peptide 1.1 ng/mL [374 pmol/L] {normal 0.9–7.1 ng/mL}). Fasting lipid profile was normal. HNF1A and HNF4A PCR followed by sequence analysis for mutations were negative. GCK analysis showed a novel heterozygous mutation p.Gln219Ter (c.655C>T) (Ambry Genetics Laboratory, California, USA). This variant results from a C to T substitution at nucleotide position 655 in exon 6 (NM_000162.3), changing glutamine to a stop codon. Her father was found to have the same mutation (Ambry Genetics). Mother and brother tested negative for the mutation (Seattle Children's Hospital Laboratory, Seattle, Washington, USA). All GCK analyses were performed by DNA amplification through PCR followed by full GCK sequencing from sense and anti sense directions.

While waiting for the genetic analyses the patient was prescribed 20 mg gliclazide once daily. The gliclazide dose, titrated to obtain the most acceptable BG range with the least symptoms was 20 mg twice daily and provided an average BG of 139 ± 16 mg/dL [7.7 ± 0.89 mmol/L; mean ± standard deviation] compared with 158 ± 32 mg/dL [8.8 ± 1.7] pre-gliclazide. She has remained on this gliclazide dose for the past 2 years with HbA_{1c} levels ranging from 5.7–6.2% (most recently 5.8%). She is now asymptomatic with the exception of occasional shakiness when BG is above 151 mg/dL [8.4 mmol/L], having noted that these episodes occur primarily with exercise and/or when she misses a dose of gliclazide. She returned to her athletic training and remains an elite-level competitive athlete. Further improvement in BG levels was reported after changing her diet to include higher protein and lower carbohydrate content.

4. Continuous glucose monitoring

To further elucidate gliclazide's effect on BG levels and symptoms, blinded continuous glucose monitoring (CGM) was completed over two separate six-day periods (iPro2, Medtronic). During the first CGM recording ("full gliclazide"), gliclazide was continued at 20 mg twice daily with 100% adherence by patient-report. She competed in an elite-level hockey tournament during this week. She was then asked to omit gliclazide for a second CGM recording but found she could not tolerate more than two days due to symptoms associated with hyperglycaemia. Therefore, the second iPro2 recording ("intermittent gliclazide") involved two days without gliclazide, followed by two days with gliclazide 20 mg bid, and then two days without gliclazide. Reported carbohydrate intake was similar during the two periods. CGM glycaemic profiles for the two periods were compared using a two-sample unequal variance t-test.

Mean average sensor glucose (SG) (mmol/L) was significantly lower during the full gliclazide period (111 ± 11 mg/dL [6.16 ± 0.61 mmol/L] vs. 129 ± 15 mg/dL [7.14 ± 0.84 mmol/L], $P = 0.03$). Time spent in the hyperglycaemic range (number of minutes per day with SG > 144 mg/dL [8 mmol/L]) and area under the curve (AUC) for sensor glucose above 144 mg/dL were also significantly less when on full vs. intermittent gliclazide (53.6 ± 0.0 minutes/day vs. 307.9 ± 246.6, $P = 0.04$ and 0.02 ± 0.04 vs. 0.22 ± 0.15, $P = 0.01$, respectively) (Table 1). There were no significant differences in the time spent in the hypoglycaemic range (< 72 mg/dL [4 mmol/L]) or AUC below 72 mg/dL (4 mmol/L). She reported no symptoms related to hypo- or hyperglycaemia during the full gliclazide period while reporting being extremely tired on the days off gliclazide and feeling shaky with a glucometer BG of 144 mg/dL (8 mmol/L).

5. Discussion

The glucokinase enzyme acts as a glucose sensor as it phosphorylates glucose to glucose-6-phosphate in the first step of glycolysis with an activity, which is in large measure mediated by glucose concentration. It is the key regulator of insulin secretion in the pancreatic β cells. Mutations in GCK shift the set point for glucose stimulated insulin release from ~ 90 to ~ 126 mg/dL (~ 5 to ~ 7 mmol/L), resulting in elevated fasting BG levels 99–144 mg/dL (5.5–8 mmol/L) with a small increment in 2-h plasma glucose (< 54 mg/dL [3 mmol/L] in 70% of patients) after a 75-g oral glucose tolerance test. GCK-MODY is generally considered a phenotypically mild, asymptomatic and non-progressive form of diabetes that does not respond to oral hypoglycaemic agents or insulin [1–4].

Our patient has a confirmed novel mutation in the *GCK* gene, as does her father. Her biochemical profile at presentation was largely consistent with that previously reported for GCK-MODY: mild fasting hyperglycaemia; small increment in 2-hour glucose in response to 75-g oral glucose tolerance test; and a dominant inheritance pattern with her father, paternal uncle, grandmother and great-grandmother all affected. The HbA_{1c} at presentation (6.7%) was higher than usually reported for

Table 1
Comparison of glycaemic profile with continuous glucose monitoring on full versus intermittent gliclazide[a].

Mean values ± SD	Full gliclazide (20 mg bid)	Intermittent gliclazide	*P*-value
Number of sensor glucose values	1791	1736	N/A
Average sensor glucose in mg/dL (mmol//L)	111 ± 11 (6.16 ± 0.61)	129 ± 15 (7.14 ± 0.84)	0.03
MAD%	13.39 ± 9.54	12.47 ± 5.13	0.73
Minutes/day with SG > 140 mg/dL (8 mmol/L)	53.6 ± 90.0	307.9 ± 246.6	0.04
AUC above 140 mg/dL (8 mmol/L)	0.02 ± 0.04	0.22 ± 0.15	0.01
Minutes/day with SG < 72 mg/dL (4 mmol/L)	14.29 ± 24.4	1.43 ± 3.78	0.21
AUC below 72 mg/dL (4 mmol/L)	0 ± 0	0 ± 0	0.17
Minutes/day within target SG of 72–140 mg/dL (4–8 mmol/L)	1211.43 ± 368.8	935 ± 392.8	0.2

AUC: area under the curve; MAD: mean absolute difference; N/A: not assessed; SD: standard deviation; SG: sensor glucose.
Values are shown as mean ± standard deviation.
[a] Full gliclazide defined as 20 mg bid; intermittent gliclazide defined as 2 days without gliclazide, followed by 2 days with gliclazide 20 mg bid, followed by 2 days without gliclazide as the patient could not tolerate more than two consecutive days without gliclazide.

GCK-MODY; typically HbA_{1c} in GCK-MODY is below or just above the upper limit of normal, although up to 7.5% has been reported. However, her reported symptomatology with hyperglycaemia and exercise is not consistent with the GCK-MODY phenotype, nor is her dramatic response to low dose Gliclazide confirmed both with self-blood glucose monitoring and blinded CGM. Loomba-Albrecht et al. [5] recently described a different novel GCK mutation that was also responsive to low dose oral sulfonylurea However, to our knowledge, ours is the first reported case of MODY-GCK presenting with exercise-induced symptomatic hyperglycaemia, with responsiveness to low dose sulfonylurea confirmed by CGM. Exercise training is known to reduce glucose stimulated insulin release (GSIR) both in vivo and in vitro. The mechanism by which exercise reduces GSIR remains unclear. However, animal studies have demonstrated that exercise significantly reduces GCK activity, and GLUT2 protein expression [6]. The resulting hypoinsulinemic state may inhibit glucose uptake given insulin's role in translocation of GLUT4 to the muscle membrane [7]. The inhibitory effect of exercise on an already decreased GCK activity may explain the hyperglycaemia observed with exercise in this elite-level athlete.

Her father shares the same GCK mutation but with a distinct clinical presentation, similar to that of his brother, mother and grandmother. All four family members were diagnosed with type 2 diabetes; none were competitive athletes. Clinical variability has been reported amongst individuals with the same GCK mutation, even within the same family [2,8]. Further, as observed in our family, the misdiagnosis of GCK-MODY as type 2 diabetes is common, frequently leading to inappropriate or ineffective treatment [1].

Klupa et al. [9] used blinded continuous glucose monitoring in 7 adults heterozygous for known GCK mutations to examine the effect on glycaemia of alterations in dietary carbohydrate content. Switching from high to low carbohydrate diet (60% vs. 25% of daily caloric intake) significantly reduced mean glucose levels and time spent in the hyperglycaemic range (BG > 140 mg/dL [7.8 mmol/L]). Furthermore, 5 of the 7 subjects had episodes of postprandial hyperglycaemia (BG > 200 mg/dL [11.1 mmol/L] for more than 15 minutes) when on the high carbohydrate diet, compared with no episodes on the low carbohydrate diet. This relationship between glycaemia and carbohydrate intake in MODY-GCK may partly explain the exercise-induced high BG levels experienced by our patient, an elite-level competitive athlete, given her tendency to consume extra carbohydrates prior to vigorous training or competition and supported by the reported improvement of her BG levels with lowering of carbohydrate intake.

We hypothesize that the patient's self-reported hypoglycaemic symptoms were related to the rate of decrease in blood glucose rather than actual hypoglycaemia. This phenomenon was observed by Simpson et al. [10] who demonstrated through CGM that only 5% of the postprandial hypoglycaemic symptoms reported by 20 otherwise healthy women were related to an interstitial BG of ≤ 60 mg/dL [3.3 mmol/L]. They observed that 32% of the reported episodes were preceded by a significant fall in glucose and concluded that a drop in glucose may lead to autonomic hypoglycaemic-like symptoms.

Although typically asymptomatic, mild and non-progressive, this adolescent's presentation suggests that MODY-GCK may not be a benign condition in the context of regular strenuous physical activity and high carbohydrate intake. Further studies are required to examine the relationship between exercise, carbohydrate intake and glycaemia in individuals with MODY-GCK.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data (French summary) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.12.012.

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