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Diabetes & Metabolism 40 (2014) 310–313

Short report

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

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Received 20 November 2013; received in revised form 22 December 2013; accepted 27 December 2013
Available online 3 February 2014

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.

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http://dx.doi.org/10.1016/j.diabet.2013.12.012

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