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Adolescent non-adherence reveals a genetic cause for diabetes

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Abstract

Background—*GCK*-MODY is a form of monogenic diabetes characterized by mildly elevated fasting blood sugars and HbA_{1c} typically ranging from 38 to 60 mmol/mol (5.6–7.6%). It is frequently unrecognized or misdiagnosed as Type 1 or Type 2 diabetes, resulting in unnecessary pharmacologic therapy.

Case report—Two brothers were initially diagnosed with Type 1 diabetes mellitus. The brothers were maintained on a total daily insulin dose of 0.3–0.5 units/kg/day and had HbA_{1c} values of 40–51 mmol/mol (5.8–6.8%) throughout childhood. After over 10 years of insulin treatment, the younger brother chose to discontinue his insulin therapy without informing his family or his clinician. Following cessation of insulin treatment, he did not experience any change in overall glycaemic control. Subsequent research-based genetic testing revealed a deleterious mutation in *GCK* in both brothers (p.Val182Met). The older brother subsequently discontinued insulin therapy and both have remained off all pharmacological therapy with good glycaemic control (HbA_{1c} < 53 mmol/mol, < 7%) and no adverse complications. The family was advised to seek confirmatory genetic testing in the father and other relatives with hyperglycaemia.

Conclusion—The family described above exemplifies the rationale behind considering a genetic cause when evaluating every person with new-onset hyperglycaemia or those with atypical diabetes. The cost of genetic testing for the most common maturity-onset diabetes of the young (MODY)-causing genes may be offset by savings made in therapeutic costs. It is important that all clinicians supervising diabetes care recognize the cardinal features that distinguish *GCK*-MODY from other forms of diabetes.

Introduction

GCK-MODY or maturity-onset diabetes of the young (MODY2) is caused by heterozygous mutations in *GCK*, which encodes glucokinase, the first enzyme in the glycolytic pathway. Glucokinase plays an important role in the ability of the β-cell to react to changes in plasma glucose concentration. Individuals with a heterozygous *GCK* mutation present with mild elevations in fasting blood glucose as a result of a shift in the glucose/insulin secretion dose–

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None declared.

response curve [1]. Blood glucose remains tightly regulated, but at concentrations higher than those seen in individuals without diabetes. Here, we describe the clinical course and implications of a *GCK*-MODY diagnosis in brothers originally thought to have Type 1 diabetes.

Case report

Brother 1 (B1) was referred to the emergency room at 4 years of age following incidental discovery of glycosuria during a routine school physical. He was admitted overnight and commenced on 4 units/day of NPH insulin for a presumptive diagnosis of Type 1 diabetes. There was no history of polyuria, polydipsia or weight loss. His dose of once-daily NPH was titrated and maintained at a dose of 0.4–0.5 units/kg/day. Mealtime insulin was prescribed, but never required. His glycaemic control remained stable with fasting glucoses of 6.1–7.8 mmol/l (110–140 mg/dl) and HbA_{1c} ranging from 40 to 48 mmol/mol (5.8–6.5%). Hypoglycaemic episodes were infrequent, mild and associated with missed meals or vomiting. He was never admitted with hyperglycaemia, ketosis or hypoglycaemia.

Brother 2 (B2), B1's younger brother, was also noted to have glycosuria at 4 years of age during a routine examination. Repeated fasting blood glucose levels were recorded at 7.2–7.8 mmol/l (110–140 mg/dl). He was commenced on 3 units/day of NPH insulin as an outpatient. His NPH insulin doses were titrated and maintained at 0.3–0.45 units/kg/day. Mealtime insulin was prescribed but only given a few times each month. His glycaemic control remained stable with fasting glucose levels of 6.1–7.8 mmol/l (110–140 mg/dl) and HbA_{1c} ranging from 42 to 51 mmol/mol (6–6.8%).

The past medical history of both boys was unremarkable. Both were born at full term; B1 weighed 3487 g (47th percentile) at birth, whereas B2 weighed 3884 g (75th percentile). Family history included impaired fasting glucose in the father and a diagnosis of Type 2 diabetes in their maternal grandfather at 60 years of age.

At age 14 years, B2 discontinued his insulin without the knowledge of his family or his clinician. Eleven months later this change was reported to his physician. There was no significant change to his HbA_{1c} or fasting blood glucose after cessation of insulin therapy (HbA_{1c}: 44–51 mmol/mol, 6.2–6.8%; blood sugar: 5.5–8.0 mmol/l, 100–145 mg/dl).

At this time, a monogenic form of diabetes was suspected. However, insurance coverage for genetic testing was denied. The family was directed to the Monogenic Diabetes Registry given the history of atypical familial hyperglycaemia (http://monogenicdiabetes.uchicago.edu). Using an in-house custom designed HaloPlex PCR enrichment system (Agilent Technologies, Santa Clara, CA, USA), sequencing was performed by standard Illumina paired-end primers and chemistry on the Illumina MiSeq platform (Illumina, Inc., San Diego, CA, USA). B2 was found to have a previously described p.Val182Met heterozygous deleterious mutation in the *GCK* gene [2]. Sanger sequencing confirmed that the mutation was also present in his brother B1, who subsequently discontinued insulin therapy with stable glycaemic control. They remain off all pharmacological therapy with good glycaemic control (HbA_{1c} < 53 mmol/mol, < 7%) and

no adverse complications. The family was advised to seek confirmatory genetic testing in the father and other relatives with hyperglycaemia.

Discussion

The incidence of Type 1 diabetes mellitus is rising in paediatric populations [3].

The degree of hyperglycaemia and frequency of ketoacidosis at initial presentation of those with Type 1 diabetes has steadily fallen and offers an opportunity for physicians to intervene with insulin treatment at an earlier disease stage [4]. Prompt insulin replacement therapy can potentially preserve β-cell function and has been associated with decreased incidence of microvascular complications [5,6]. Although early insulin therapy has clear benefits for those with Type 1 diabetes, our case highlights how this might result in inappropriate therapy when initial diabetes classification is incorrect.

Maturity-onset diabetes of the young (MODY) is a heterogeneous group of dominantly inherited forms of diabetes that are usually diagnosed before 30 years of age, accounting for 1–2% of all people with diabetes [7]. MODY can be difficult to distinguish from Type 1 and Type 2 diabetes, but should be considered in any individual carrying a diagnosis of either type of diabetes and presenting with atypical features [8]. Variable awareness of MODY and unequal access to genetic testing are potential reasons that the majority of those with MODY go unrecognized [9]. The three common forms of MODY (MODY1, -2 and -3) are estimated to represent at least 1.2% of all paediatric diabetes cases in the USA [10] with *GCK*-MODY the second most common MODY subtype found.

Deleterious heterozygous mutations in *GCK* causing *GCK*-MODY occur at a frequency of ~ 1 in 1000 of the general population [11]. *GCK*-MODY results in mildly elevated fasting glucose ranging from 6.1 to 7.8 mmol/l (110–140 mg/dl) and postprandial sugars that rarely rise above 13.9 mmol/l (250 mg/dl) [1]. Those with *GCK*-MODY have HbA_{1c} values that normally range from 38 to 60 mmol/mol (5.6–7.6%) and may be inappropriately treated with insulin or with oral hypoglycaemic agents [12]. However, neither treatment with insulin nor treatment with oral hypoglycaemic agents will significantly decrease HbA_{1c} [13]. Steele *et al*. noted that the prevalence and severity of vascular disease was markedly different from that typically associated with Type 1 or Type 2 diabetes when they assessed 99 individuals with *GCK* mutations aged 35 years and older [12]. A low prevalence of macrovascular disease was seen in those with *GCK*-MODY and was similar to that of controls. The rates of nephropathy and neuropathy did not differ from controls. However, there was an increase in background retinopathy, but none of the participants with *GCK*-MODY were found to have proliferative retinopathy despite a median duration of 48.6 years of hyperglycaemia.

The cost of genetic testing for the most common MODY-causing genes may be offset by savings made in therapeutic costs. Indeed, modelling data has suggested that genetic testing for MODY1, -2 and -3 in appropriately selected populations may potentially be cost-effective [14]. Genetic testing continues to become more affordable and in the future should afford hundreds of thousands of Americans an opportunity to have inexpensive genetic testing [15]. Therefore, it is important that all clinicians supervising diabetes care recognize

the cardinal features that distinguish *GCK*-MODY from other forms of diabetes. There are differences in clinical phenotype that indicate a monogenic, rather than autoimmune aetiology. Asymptomatic or incidentally found hyperglycaemia in children is frequently due to *GCK*-MODY and should cause clinicians to consider a monogenic aetiology [16]. Negative pancreatic antibodies in those suspected to have Type 1 diabetes, particularly with history of familial diabetes, should alert providers to a potential genetic rather than autoimmune pathology [8]. Clinical clues and appropriate targeted investigations can aid in appropriate selection of patients for genetic testing (Table 1).

Despite *GCK*-MODY being discovered over 20 years ago, it frequently goes unrecognized [9,17]. The family described above exemplifies the rationale behind considering a genetic cause when evaluating every person with new-onset hyperglycaemia or those with atypical diabetes. Persons with *GCK* mutations, in particular, stand to benefit greatly from a correct diagnosis given the frequency of mutations in the general population and the personal and financial benefits associated with discontinuing therapy.

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What's new?

- *GCK*-MODY continues to be misdiagnosed and improperly treated, unnecessarily driving up the costs of diabetes care.
- *GCK*-MODY can be accurately identified based on simple clinical criteria.
- A genetic cause should be considered when evaluating every person with new-onset hyperglycaemia.
- Clinical genetic testing should be more readily available for the 1 in 1000 individuals affected by *GCK*-MODY.

Table 1

Clinical features of the common forms of MODY

Cardinal features suggestive of all types of MODY
Hyperglycaemia diagnosed at < 30 years of age
Nonobese and no evidence of insulin resistance
> 2 Linear generational family history of hyperglycaemia
Negative pancreatic auto-antibodies (GAD, IAA, ICA, ZnT8)
Features suggestive of *GCK*-MODY (MODY 2)
Stable HbA_{1c} < 62 mmol/mol (< 7.8%)
Mild fasting hyperglyacemia from birth
Features suggestive of *HNF4A/1A*-MODY (MODY 1/3)
Positive serum or urine C-peptide 3–5 years after initial diagnosis [18]
Sensitivity to sulfonylurea therapy