CASE REPORT

A glucokinase gene mutation in a young boy with diabetes mellitus, hyperinsulinemia, and insulin resistance

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Abstract: We report the case of a 12-year-old boy with a glucokinase (*GCK*) mutation, and diabetes with hyperinsulinemia and insulin resistance. For 4 years, the patient intermittently received insulin medications Actrapid HM and Protaphane HM (total dose 5 U/day), with glycated hemoglobin (HbA_{1c}) levels of 6.6%–7.0%. After extensive screening the patient was found to carry a heterozygous mutation (p.E256K) in *GCK* (MIM #138079, reference sequence NM_000162.3). Insulin therapy was replaced by metformin at 1,700 mg/day. One year later, his HbA_{1c} level was 6.9%, postprandial glycemia at 120 min of oral glucose tolerance test was 15.4 mmol/L, hyperinsulinemia had increased to 508.9 mU/L, homeostasis model assessment index was 114.2 and the Matsuda index was 0.15. Insulin resistance was confirmed by a hyperinsulinemic euglycemic clamp test – M-index was 2.85 mg/kg/min. This observation is a rare case of one of the clinical variants of diabetes, which should be taken into account by a vigilant endocrinologist due to the need for nonstandard diagnostic and therapeutic approaches.

Keywords: case report, insulin resistance, diabetes mellitus, MODY2, child

Introduction

Maturity-onset diabetes of the young (MODY) is a group of monogenic heterozygous diseases caused by mutations in more than 13 different genes, resulting in disruption of insulin secretion.[1] Specifically, heterozygous mutations in the glucokinase gene (*GCK*) may lead to MODY type 2 (MODY2), which is one of the most common forms of MODY in a number of countries in Europe and Russia,[2–4] and presents diverse phenotypes.[5] Previously, it was believed that insulin resistance (IR) is characteristic only for diabetes mellitus type 2 (DM2), but recently, there have been reports of possible IR in patients with MODY.[6,7]

In this paper, we present a clinical case of a patient with DM with a glucokinase (*GCK*) mutation and significant IR.

Case report

A 12-year-old Caucasian male patient presented with a diagnosis of unspecified DM. At the age of 8, it was incidentally discovered that the patient had fasting hyperglycemia (7.7 mmol/L) without clinical symptoms. The oral glucose tolerance test (OGTT) showed glucose levels at baseline and 120 min of 6.6 and 12.1 mmol/L, respectively. Other findings included the absence of glycosuria and glycated hemoglobin (HbA_{1c}) level of 6.4%. The patient was diagnosed with DM type 1 (DM1) and prescribed Actrapid HM (3 U/day; NovoNordisk A/S, Bagsværd, Denmark) and Protaphane

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HM (2 U/day; NovoNordisk A/S). The daily glucose levels were 4.0−8.6 mmol/L and his HbA$_{1c}$ levels ranged between 6.6%–7.7% for 4 years.

At the time of admission (12-years-old), the body mass index and height both expressed with standard deviation (SD) were 17.3±0.21 kg/m^2 and 148.6±0.28 cm, respectively. No signs of acanthosis were observed. The daily insulin dose was 5 U (0.13 U/kg), blood glucose fluctuated from 4.1 to 8.2 mmol/L, and glycated hemoglobin was 7.0%. There were no signs of dyslipidemia. The OGTT demonstrated impaired glucose tolerance (6.5 mmol/L at baseline, 8.9 mmol/L on 120 min), pronounced hyperinsulinemia (immunoreactive insulin [IRI] from 321.3 mU/L up to 442.1 mU/L), and IR (Caro index 0.02 [normal >0.2], homeostasis model assessment [HOMA] 92.82 [normal <3.4]).

Glutamic acid decarboxylase, islet cell, insulin, and tyrosine phosphatase antibodies were negative. Typing for HLA-protective haplotypes revealed the presence of DM1 protective haplotypes DRB1*1313, DQA1*0103, and DQB1*0602-8. The patient had no family history of glucose metabolism disorders (Figure 1).

Considering the mild course of the disease during the previous 4 years, despite pronounced IR, the *GCK* nucleotide sequence was analyzed using polymerase chain reaction followed by direct sequencing. A heterozygous mutation (p.E256K) was identified in *GCK* (MIM #138079, reference sequence NM_000162.3). After the genetic testing, insulin therapy was cancelled and metformin (1,000 mg/day) was prescribed.

The patient's parents also had molecular genetic testing done. The nucleotide sequence of exon 7 of *GCK* (Gene ID 2645) was analyzed using polymerase chain reaction followed by direct sequencing. There were no mutations in the nucleotide sequence of exon 7. Because of ethical considerations, genetic paternity test was not performed.

A year later, patient parameters were assessed: 1) height (SD), 155.4 cm (0.05); 2) body weight, 44 kg; 3) body mass index (SD), 18.22 kg/m^2 (0.0); and 4) Tanner development, stage 4. The blood glucose ranged from 6.4 to 10.1 mmol/L. HbA$_{1c}$ level was 6.9%. According to his OGTT results, there was deterioration of glucose metabolism (glycemia after 2 h was 15.4 mmol/L), hyperinsulinemia increased (up to 508.9 mU/L) and IR (HOMA index 114.26, Matsuda index 0.15) (Table 1). During a mixed-meal glucose tolerance test, the glycemic rate was high. However, daily fluctuations of the blood glucose were between 6.4 and 10.1 mmol/L, which corresponded with an HbA$_{1c}$ of <7%.

A hyperinsulinemic euglycemic clamp test, the gold standard for the study of IR, was performed for the patient.

The rate of insulin infusion in this patient was 1.0 mU/kg/min, and the M-index (glucose disposal rate) was 2.85 mg/kg/min. For adults, a normal M-index is >6.0 mg/kg/min, and a value <2 mg/kg/min indicates a moderate IR. There is no established normal range for adolescents. Even taking into account the physiological IR of adolescence, we considered these results

Table 1 The results of OGTT 1 year after the initial survey

Time, min	0	30	60	90	120
Glucose, mmol/L	6.4	11.0	13.1	14.6	15.4
IRI, mU/L	401.7	475.0	481.7	508.9	487.4

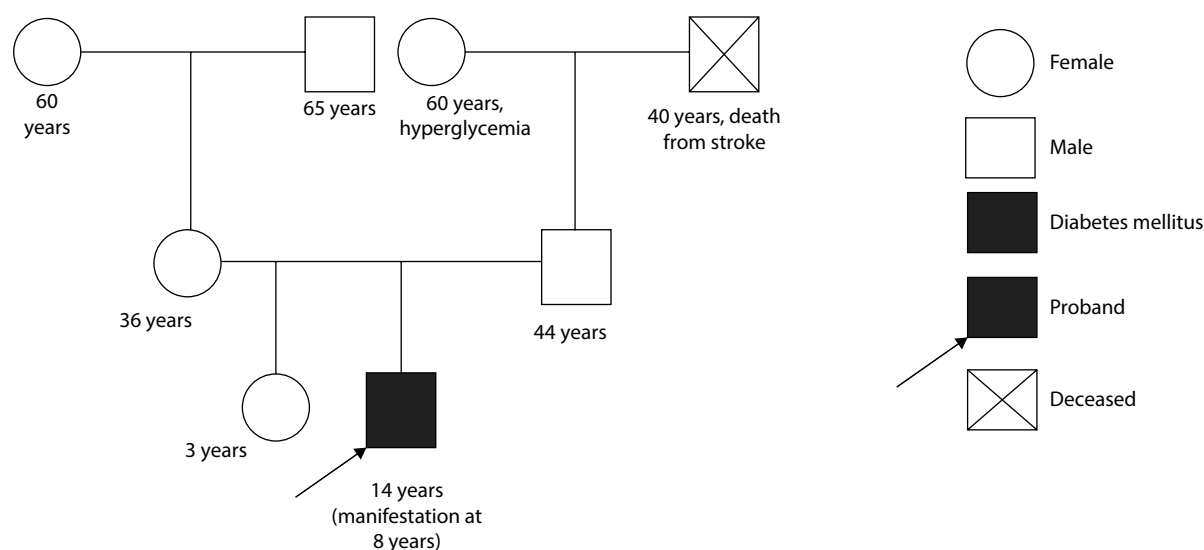**Abbreviations:** IRI, immunoreactive insulin; OGTT, oral glucose tolerance test.

Figure 1 Genealogical analysis.

Table 2 OGTT results 18 months after beginning metformin treatment

Time, min	0	60	120
Plasma glucose, mmol/L	5.9	16.2	16.2
IRI, mU/L	430.4	501	508.4

Abbreviations: IRI, immunoreactive insulin; OGTT, oral glucose tolerance test.

to confirm IR in our patient. A hyperinsulinemic–euglycemic clamp test confirmed the presence of IR in this patient.

Owing to the increased IR, metformin dose was increased to 1,700 mg/day. After 6 months from increasing the dose, the glycemic profile showed no significant improvement of glycemic control. The HbA$_{1c}$ level was 6.6% and an OGTT demonstrated increased glycemia and IRI after 60 and 120 min without significant changes in IR (HOMA index was 112.86, Matsuda index 0.12) (Table 2).

The following genes were analyzed on an Ion Torrent sequencing system with a custom DM-HI (monogenic forms of diabetes, hyperinsulinism) AmpliSeq panel: *GCG*, *GLUD1*, *WFS1*, *HNF1A*, *GCK*, *INS*, *HNF1B*, *ABCC8*, *HNF4A*, *RFX6*, *PTF1A*, *NEUROD1*, *AKT2*, *ZFP57*, *INSR*, *EIF2AK3*, *PPARG*, *PAX4*, *PDX1*, *GLIS3*, *KCNJ11*, *SLC16A1*, *FOXP3*, *BLK*, *CEL*, *KLF11*, *SCHAD* and *GCGR* (total coverage 96.5%). The analysis showed the presence of the same p.E256K mutation in *GCK* gene. Thus, the diagnosis of MODY2 can be confirmed by performing molecular genetic testing twice. There were no mutations in other tested genes, including *INSR* and *PPARG*. We did not test for mutations in other genes such as those responsible for lipodystrophy-associated insulin resistant diabetes mellitus, including gene *LMNA*, because there were no clinical signs of lipodystrophy.

Discussion

The presented case of diabetes in a young boy with a *GCK* mutation, with increasing hyperinsulinemia and IR results recorded during 18 months of observation is a vivid clinical illustration of mutation-associated IR confirmed by hyperinsulinemic euglycemic test. The course of diabetes was mild, with no need for insulin injections and no effect of biguanide drugs.

The diagnosis of MODY2 was confirmed twice by molecular genetic testing. The absence of a family history of this gene indicated a de novo mutation in the child. The proband mutation, p.E256K, in the gene *GCK* was described in 1993 by Gidh-Jain et al and was shown to cause non-insulin dependent DM.[8] This mutation, p.E256K, is rare in a population (8.29×10^{-6}).[9] However, the p.E256K mutation has

been described in several cases: two families in Spain;[10] three families in Sweden;[3] and five families in the Netherlands[3].

The high IRI level, in combination with IR, are unusual in the known MODY subtypes. In a small study, Guenat et al demonstrated that IR may be present in MODY2 and may be caused by counter-regulatory responses to hyperglycemia because of an increase in glucagon secretion and activation of gluconeogenesis in the liver.[11] Clément et al showed lower insulin sensitivity in MODY2 compared with a healthy control group (glucose infusion rate 3.38+3.10 vs 8.08+3.79 mg×kg bw^{-1}×min^{-1} [P=0.005]).[12]

Usually in children and adolescents without glucose metabolism impairment and with MODY2 a pubertal increase in insulin secretion is observed, but it is lower than that in the described case.[13,14] Despite a high insulin level, a discrepancy between high HOMA index of IR and mild IR levels according to the hyperinsulinemic–euglycemic clamp test was evident.

Measured IRI levels were significantly higher than those seen in DM2. At the onset of DM2 in adolescents, insulin levels (median [Q25; Q75]) were 19.3 mcU/mL (12.0, 33.7), 105.6 mcU/mL (67.2, 176.9), and 154.3 mcU/mL (70.6, 236.2) at 0, 60, and 120 min during OGTT, respectively.[15]

Simultaneous presence of a *GCK* mutation and IR in a patient with DM is extremely intriguing, and a nosological interpretation of the case remains unclear. The development of MODY2 in combination with DM2, or a direct connection between the mutation and development of DM2, cannot be excluded. The absence of obesity does not contradict the diagnosis of DM2 because 10%–50% of both children and adolescents with DM2 are not obese in different populations.[15]

It is unclear how the defective β-cells could respond by production of such high insulin levels under IR conditions.

This case study and analysis of published data demonstrates the heterogeneity of clinical manifestations in some cases of *GCK*-MODY. Such rare observations generate even more interest in solving the puzzle of what appears to be the mildest form of MODY. For the practitioner, observations presented in this paper indicate the need for attention and in-depth clinical examination of each case for a mild, insulin-independent course of diabetes in children and adolescents.

Conclusion

Non-typical cases of diabetes in children require nonstandard diagnostic and treatment approaches. The combination of different causes of impaired glucose metabolism may manifest in non-typical forms of diabetes. Further studies

are required to study the potential genetic link of DM2 and MODY.

Acknowledgments

Written informed consent was obtained from the patient and patient's family for this case presentation.

Disclosure

The authors report no conflicts of interest in this work.

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