Clinical Pediatric Endocrinology

Vol.32 / No.1
January 2023
pp 72–75

Case Report

Glucokinase maturity-onset diabetes of the young as a mimicker of stress hyperglycemia: a case report

Yoshitaka Nakasato[1], Shintaro Terashita[2], Shohei Kusabiraki[1], Sadashi Horie[2], Takuya Wada[3], Motokazu Nakabayashi[4], Megumi Nakamura[5], and Tohru Yorifuji[6]

[1]*Department of Pediatrics, Itoigawa General Hospital, Niigata, Japan*
[2]*Department of Pediatrics, Toyama University Hospital, Toyama, Japan*
[3]*Department of Pediatrics, Toyama City Hospital, Toyama, Japan*
[4]*Department of Pediatrics, Hida Municipal Hospital, Gifu, Japan*
[5]*Nakamura Children's Clinic, Niigata, Japan*
[6]*Division of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka, Japan*

Highlights

- In certain patients, GCK-MODY mimics stress hyperglycemia during febrile seizures
- Detailed family history and mildly elevated HbA1c distinguish GCK-MODY

Abstract. Febrile seizures are frequently accompanied by stress-induced hyperglycemia. Herein, we report the case of a 1.5-yr-old girl with hyperglycemia during febrile seizures who was subsequently diagnosed with glucokinase (GCK) maturity-onset diabetes of the young (MODY), considering its distinction from stress hyperglycemia. Following the development of febrile seizures owing to adenovirus infection, the patient presented a casual blood glucose level was 185 mg/dL. She had a multigenerational family history of diabetes and a hemoglobin A1c (HbA1c) level of 6.4%. Owing to the persistent glucose intolerance until the age of 5 years, genetic testing was performed, which revealed a heterozygous mutation in *GCK*, and the patient was diagnosed with GCK-MODY. Precise diagnosis of GCK-MODY individuals is important to avoid administering unnecessary antidiabetic medications. Even during hyperglycemia under stress, multigenerational diabetes and mildly elevated HbA1c levels can suggest GCK-MODY.

Key words: glucokinase, stress hyperglycemia, maturity-onset diabetes of the young

Received: March 23, 2022 Accepted: November 7, 2022 Advanced Epub: December 3, 2022
Corresponding author: Shintaro Terashita, M.D., Department of Pediatrics, Faculty of Medicine, University of Toyama, 2630 Sugitani, Toyama, Toyama 930-0194, Japan
E-mail: sterashita@ped-toyama.com

Introduction

Maturity-onset diabetes of the young (MODY) 2 is a type of diabetes mellitus caused by a heterozygous loss-of-function glucokinase (*GCK*) gene mutation characterized by autosomal dominant inheritance. GCK-MODY exhibits hyperglycemia owing to insulin secretory deficit, which is mild, stable, and unrelated to hyperglycemic complications, as detected in other types of diabetes (1). Therefore, patients diagnosed with GCK-MODY should not be treated with antidiabetic drugs.

GCK-MODY can be occasionally diagnosed owing to accidentally discovered hyperglycemia. Stress hyperglycemia is associated with febrile seizures (FS) (2), a frequently experienced accidental hyperglycemia that may be facilitated by GCK-MODY. Further unnecessary administration of antidiabetic medications can be avoided if hyperglycemia leads to a diagnosis of GCK-MODY. To the best of our knowledge, this is the first case of GCK-MODY with initial symptoms of hyperglycemia during FS. In the present report, we discuss the key features to distinguish between GCK-MODY and stress hyperglycemia.

Patients and Methods

A 1.5-yr-old girl was born through a non-consanguineous marriage. The mother was confirmed to have gestational diabetes, and the grandmother was diagnosed with diabetes at 40 yr of age. Her great-grandmother and great-grandfather were also diagnosed with diabetes. The patient visited a local doctor owing to a fever (39°C) and systemic tonic seizure of approximately 1 min, resulting in a diagnosis of simple FS. The following day, the patient experienced a second seizure (approximately 1 min) with a high fever. Her casual blood glucose level during high fever was 185 mg/dL, and on the same day, a diazepam suppository was prescribed for complex FS with adenovirus infection. Following continued fever, a blood test was repeated at the clinic on illness day 3, revealing a blood glucose level of 142 mg/dL 2 h after a meal. Given that the patient had a multigenerational family history of diabetes, the hemoglobin A1c (HbA1c) level was measured and presented a value of 6.4%. The patient was referred to our hospital for a detailed examination of complex FS and impaired glucose tolerance. No evidence of ketoacidosis was detected, and the blood test showed that immunoreactive insulin (IRI) was 0.49 μU/mL for 100 mg/dL of blood glucose. After the fever resolved, the seizures did not recur, and the patient was discharged on day 5 of illness. A blood test was performed two months after the onset, revealing a fasting blood glucose level of 110 mg/dL; however, HbAlc remained elevated (6.9%). Meanwhile, IRI was 0.75 μU/mL, and homeostasis model assessment insulin resistance (HOMA-IR) was 0.2, with no increase, but the homeostasis model assessment of β-cell function (HOMA-β) was remarkably low (6%), suggesting a decrease in insulin secretion capacity. None of the anti-GAD, anti-insulin, or anti-IA-2 antibodies revealed an increase in antibody titer. The regular medical examination was continued up to approximately three years after the first admission at our clinic. During this period, the patient's condition did not exacerbate, and the HbA1c level remained at approximately 6.5%. At five years of age, the patient underwent an oral glucose tolerance test to reveal fasting blood glucose and blood glucose levels 2 h after loading within the normal range; however, HOMA-β was low (2.14), and the insulinogenic index also dropped to 0.29 (**Table 1**), again suggesting a reduced insulin secretion capacity.

Results

Given the prolonged high HbAlc levels for three years and a multigenerational family history of diabetes, MODY was suspected, genetic testing was performed, and heterozygous mutation of the *GCK* gene (c.214G>A, p.Gly72Arg) was confirmed (**Fig. 1**). The patient was diagnosed with GCK-MODY according to the American

Table 1. Oral glucose tolerance test values

	Blood glucose (mg/dL)	IRI (μU/mL)
Before loading	105	0.25
30 min	215	32.3
60 min	198	33.9
120 min	162	17
		Reference value
HOMA-β	2.14	> 30%
HOMA-IR	0.06	≤ 1.6
Insulinogenic Index	0.29	≤ 0.4 [a]

IRI, immunoreactive insulin; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance. [a] These are reference values for decreased early insulin secretion in adults. However, it has been reported that the pediatric insulinogenic index tends to decrease with age (Mean values for each age group; 1–3 yr: 0.53, 4–6 yr: 0.62, 7–11 yr: 1.10, 12–16 yr: 1.34).

doi: 10.1297/cpe.32.2022-0024

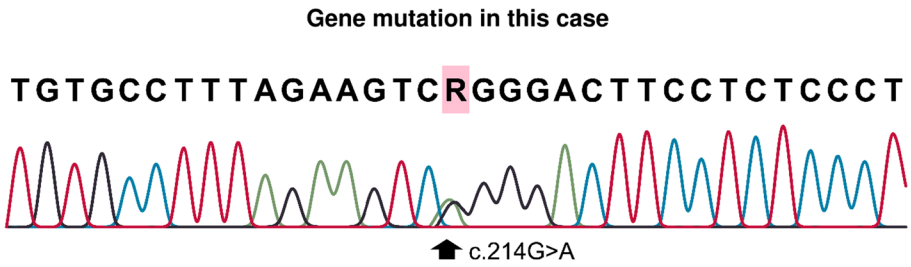

Fig. 1. Family history of diabetes mellitus and gene mutations. The genetic testing results of the present patient confirmed the heterozygous missense mutation G→A in coding DNA no. 214 of the *GCK* gene (c.214G > A p.Gly72Arg). * The mother was diagnosed with diabetes mellitus following the patient's diagnosis.

College of Medical Genetics and Genomics guidelines because several previous reports on this gene, including one from Pruhova *et al*., suggested that it could be the causative gene mutation for GCK-MODY (3). By the age of 5 yr, the patient experienced no complications of diabetes.

Written informed consent was obtained from the guardian for genetic testing and publication of this case, and the study was approved by the ethics committee of Itoigawa General Hospital.

Discussion

Without a precise diagnosis of GCK-MODY, patients may be overtreated for diabetes in the absence of progressive glucose intolerance (4). In a large survey of pharmacological treatments for pediatric patients with GCK-MODY, nearly 50% of patients were taking antidiabetic medication, including insulin, at the time of confirmed diagnosis (5). Given that GCK-MODY can be misdiagnosed as type 2 or early-stage type 1 diabetes, precise diagnosis before initiating therapy is critical to avoid compelling patients to undergo unnecessary treatment.

Although the precise diagnosis of GCK-MODY has clear advantages for patients, costs associated with genetic testing present a considerable disadvantage. The prevalence of GCK-MODY is approximately 0.1%, and genetic testing cannot be performed in all patients (6). A study investigating the cost-effectiveness of genetic testing for GCK, HNF1A, and HNF4A-MODY in patients with type 2 diabetes aged < 40 yr has estimated that the total prevalence rate of MODY must be approximately 30% to achieve cost savings (7). However, the cost-effectiveness of MODY gene testing may only be advantageous in childhood. Goodsmith *et al*. have reported that MODY genetic testing in patients with diabetes aged < 20 yr selected by biomarker screening, such as C peptide and islet antibodies, could afford cost savings over a 30-yr time horizon, which is further enhanced when combined with cascade screening (8). Considering the high penetrance of GCK-MODY and its favorable prognosis without medication, a precise diagnosis by genetic testing in early childhood may have significant advantages not only for the proband but also for the patient's family and socioeconomics if the patient selection is performed via appropriate screening.

Family history is a crucial factor in screening for GCK-MODY. Carmody *et al*. have reported that 93.9% of GCK-MODY probands have a family history of hyperglycemia (9). It is characterized by the multigenerational and early (typically < 35 yr) onset of diabetes (10). Herein, four generations of this family exhibited impaired glucose tolerance, especially the proband's mother and grandmother, who developed diabetes at an early age and could also be suspected of exhibiting MODY. Therefore, detailed family history is one of the most important factors for screening MODY in cases of accidental hyperglycemia.

In addition, biochemical markers are pivotal for screening MODY (10), among which we focused on HbA1c and insulin secretory capacity. The pathogenesis of GCK-MODY involves a high threshold for glucose-stimulated insulin secretion, and patients with GCK-MODY experience a mildly elevated HbA1c level (7.6%), reflecting persistent hyperglycemia (11). Therefore, a mild and persistently elevated HbA1c level is suggestive of GCK-MODY. Considering the insulin secretory capacity, hyperglycemia in GCK-MODY can be attributed to inappropriate insulin secretion rather than insulin resistance through upregulated catecholamine, cortisol, and inflammatory cytokines and downregulation of post-receptor insulin signaling, the underlying cause of hyperglycemia-associated FS (12, 13). Compared with the healthy prepubertal group, the present patient exhibited a relatively high glycemia/insulin ratio (204 vs. 24 [10–50]) and low HOMA-IR (0.1 vs. 0.7 [0.3–1.9]) during high fever (14). Although the patient did not present with a severe hyperglycemic state on examining IRI, it provided us an opportunity to suspect a decreased insulin secretory capacity.

The incidence of stress hyperglycemia due to FS is approximately 12.9% (15). Most FS cases occur before the age of 3 yr, which is younger than the average age at diagnosis of GCK-MODY (14.0 [7.3–26.8]) (9). Therefore, on encountering accidental hyperglycemia with FS, focusing on detailed family history and biochemical markers, such as mild and persistently elevated HbA1c, may afford a precise diagnosis of GCK-MODY before initiating unnecessary medication.

doi: 10.1297/cpe.32.2022-0024

Conclusion

A precise diagnosis of GCK-MODY is important to avoid unnecessary medication. On encountering hyperglycemia during FS, detailed family history and attention to glucose tolerance may help diagnose GCK-MODY.

Conflict of interests: The authors declare no conflict of interest.

Acknowledgments

The authors thank Crimson Interactive Pvt. Ltd. (Ulatus) (www.ulatus.jp) for their assistance with manuscript translation and editing.

References

1. Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO, *et al*. Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. Nature 1992;356: 162–4. [Medline] [CrossRef]
2. Fattorusso V, Nugnes R, Casertano A, Valerio G, Mozzillo E, Franzese A. Non-diabetic hyperglycemia in the pediatric age: Why, how, and when to treat? Curr Diab Rep 2018;18: 140. [Medline] [CrossRef]
3. Pruhova S, Dusatkova P, Sumnik Z, Kolouskova S, Pedersen O, Hansen T, *et al*. Glucokinase diabetes in 103 families from a country-based study in the Czech Republic: geographically restricted distribution of two prevalent GCK mutations. Pediatr Diabetes 2010;11: 529–35. [Medline] [CrossRef]
4. Timsit J, Saint-Martin C, Dubois-Laforgue D, Bellanné-Chantelot C. Searching for maturity-onset diabetes of the young (MODY): when and what for? Can J Diabetes 2016;40: 455–61. [Medline] [CrossRef]
5. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, *et al*. SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013;98: 4055–62. [Medline] [CrossRef]
6. Chakera AJ, Spyer G, Vincent N, Ellard S, Hattersley AT, Dunne FP. The 0.1% of the population with glucokinase monogenic diabetes can be recognized by clinical characteristics in pregnancy: the Atlantic Diabetes in Pregnancy cohort. Diabetes Care 2014;37: 1230–6. [Medline] [CrossRef]
7. Naylor RN, John PM, Winn AN, Carmody D, Greeley SA, Philipson LH, *et al*. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. Diabetes Care 2014;37: 202–9. [Medline] [CrossRef]
8. GoodSmith MS, Skandari MR, Huang ES, Naylor RN. The impact of biomarker screening and cascade genetic testing on the cost-effectiveness of MODY genetic testing. Diabetes Care 2019;42: 2247–55. [Medline] [CrossRef]
9. Carmody D, Naylor RN, Bell CD, Berry S, Montgomery JT, Tadie EC, *et al*. GCK-MODY in the US National Monogenic Diabetes Registry: frequently misdiagnosed and unnecessarily treated. Acta Diabetol 2016;53: 703–8. [Medline] [CrossRef]
10. Broome DT, Pantalone KM, Kashyap SR, Philipson LH. Approach to the patient with mody-monogenic diabetes. J Clin Endocrinol Metab 2021;106: 237–50. [Medline] [CrossRef]
11. Steele AM, Wensley KJ, Ellard S, Murphy R, Shepherd M, Colclough K, *et al*. Use of HbA1c in the identification of patients with hyperglycaemia caused by a glucokinase mutation: observational case control studies. PLoS One 2013;8: e65326. [Medline] [CrossRef]
12. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet 2009;373: 1798–807. [Medline] [CrossRef]
13. Costea RM, Maniu I, Dobrota L, Neamtu B. Stress hyperglycemia as predictive factor of recurrence in children with febrile seizures. Brain Sci 2020;10: 131. [Medline] [CrossRef]
14. Ballerini MG, Bergadá I, Rodríguez ME, Keselman A, Bengolea VS, Pipman V, *et al*. Insulin level and insulin sensitivity indices among healthy children and adolescents. Arch Argent Pediatr 2016;114: 329–36 (in Spanish). [Medline]
15. Valerio G, Franzese A, Carlin E, Pecile P, Perini R, Tenore A. High prevalence of stress hyperglycaemia in children with febrile seizures and traumatic injuries. Acta Paediatr 2001;90: 618–22. [Medline] [CrossRef]

doi: 10.1297/cpe.32.2022-0024