JCEM Case Reports, 2023, **1**, 1–3
https://doi.org/10.1210/jcemcr/luad032
Advance access publication 6 April 2023
Case Report

Persistent Hypoglycemia and Hyperinsulinism in a Patient With *KMT2D*-Associated Kabuki Syndrome

Mariana Nunez Stosic[1] **and Patricia Gomez**[1]

[1]Pediatric Endocrinology, University of Miami, Miami, FL 33136, USA

Correspondence: Mariana Nunez Stosic, MD, Pediatric Endocrinology, University of Miami, 1601 NW 12th Avenue, Miami, FL 33136, USA.
Email: marnusto@gmail.com.

Abstract

We report a 3-year-old girl with persistent hypoglycemia and hyperinsulinism secondary to *KMT2D*-associated Kabuki syndrome (KS). During the neonatal period, the patient had multiple complications, including gastroesophageal reflux disease, failure to thrive, G-tube dependence, congenital heart disease, and persistent hypoglycemia. The initial workup at 2 weeks of age was suggestive of hyperinsulinism. She was treated with intravenous glucose infusion and diazoxide. She was discharged from the NICU on diazoxide, chlorothiazide, and enteral feeds. Diazoxide was discontinued at 2 months old secondary to adverse effects. Hyperinsulinemic hypoglycemia was ultimately confirmed with a glucagon stimulation test at 5 months of age. At 11 months of age, when the enteral feeds were attempted to be spaced, she presented to our outpatient clinic with persistent hypoglycemia. Review of prior outside records confirmed a negative congenital hyperinsulinism genetic panel. She was treated with maltodextrin, enteral feeds, and close glucose monitoring. We noted that she had dysmorphic features that were suggestive of KS. At 2 years of age, a whole exome sequence confirmed a pathogenic mutation in *KMT2D*. Persistent hypoglycemia beyond the neonatal period is a rare finding in KS. In addition, it is a more common finding in KS type 2 (*KDM6A*).

Key Words: hypoglycemia, Kabuki syndrome, hyperinsulinism, *KMT2D*

Abbreviations: BG, blood glucose; HH, hyperinsulinemic hypoglycemia; KS, Kabuki syndrome; NICU, neonatal intensive care unit.

Introduction

Kabuki syndrome (KS) is a disease characterized by distinctive facial features, skeletal anomalies, and delay in neuromotor development. Hypoglycemia, congenital heart disease, hypotonia, and gastrointestinal problems are seen infrequently [1]. KS is rare, with a prevalence about 1:32 000 [2]. *KMT2D*-associated KS (type 1) is an autosomal dominant condition and *KDM6A*-associated KS (type 2) is an X-linked disorder [1]. Hyperinsulinemic hypoglycemia (HH) is present in 0.3% of KS patients, in which the majority have *KDM6A* -related KS [1]. The hyperinsulinism is presumed to be secondary to dysregulated insulin secretion, but the exact mechanism is not fully understood, especially in *KMT2D*-associated KS [3].

Case Presentation

Our female patient, now 3 years old, was diagnosed with *KMT2D*-associated KS at 2 years of age. Diagnosis was suspected secondary to characteristic facial features, developmental delay, feeding difficulties, and persistent hypoglycemia. She was born at 37 weeks of gestation via emergency cesarean delivery due to a history of maternal preeclampsia. Apgar scores were 3/6/8 at 1, 5, and 10 minutes of life, respectively. Birth weight was 3090 grams. Delivery was complicated by meconium aspiration syndrome, for which the patient was admitted to the neonatal intensive care unit (NICU) where she had a prolonged course. During the neonatal period, she had multiple complications including gastroesophageal reflux disease (GERD), failure to thrive requiring G-tube placement without Nissen fundoplication, recurrent urinary tract infections, congenital heart disease (mild right ventricular hypertrophy, atrial septal defect) and persistent hypoglycemia. Hypoglycemia was presumed to be a result of perinatal stress–induced hyperinsulinism at that time. Diazoxide and chlorothiazide were started with a good response but had to be discontinued at 2 months of age due to noted pulmonary hypertension during a subsequent admission for respiratory failure. Blood glucose levels (BGs) at this time were above goal and she was able to be safely managed with frequent enteral feeds.

At 5 months of age, she had a hypoglycemic episode at home of 43 mg/dL. BG was 56 mg/dL on arrival to the emergency department. She was admitted and hyperinsulinism was confirmed at this time with a glucagon stimulation test. She was successfully treated with increased frequency of the feeds. At 11 months of age, she was referred to our clinic by the gastroenterology team for inability to space enteral feeds. At home, the BG level ranged from 57 to 77 mg/dL on bolus feeds every 3 hours. Cornstarch was started by our team, but ultimately had to be changed to maltodextrin, given development of diarrhea. She has successfully been managed to date with maltodextrin.

Diagnostic Assessment

The evaluation at 2 weeks of life was suggestive of hyperinsulinism with a critical sample remarkable for a BG of 57 mg/dL, an insulin level of 8.03 uIU/mL, and a cortisol of 0.4 ug/dL. A

Received: 28 October 2022. **Editorial Decision:** 7 March 2023. **Corrected and Typeset:** 6 April 2023

cosyntropin (15 mg) stimulation test was performed. The cortisol level was 22.3 ug/dL at 30 minutes after the administration of cosyntropin, excluding adrenal insufficiency as the cause of the persistent hypoglycemia.

During the admission at 5 months of age for hypoglycemia, a supervised fast followed by a glucagon stimulation test was performed. After 17 hours of fasting, the patient developed hypoglycemia with a point-of-care glucose of 49 mg/dL. A critical sample was obtained, which was remarkable for a beta-hydroxybutyrate of 1.27 mmol/L, a plasma glucose level of 52 mg/dL, a growth hormone level of 9.7 ng/mL, and an insulin level of 2 uIU/mL. Intravenous glucagon was administered. Point-of-care glucose level 40 minutes later was 95 mg/dL, suggestive of hyperinsulinism.

During our outpatient evaluation at 11 months of age, a review of outside records showed that she had a negative congenital hyperinsulinism genetic panel, which tested for the most frequent mutations (*ABCC8, GCK, GLUD1, KCNJ11)*. She had features that were suggestive of a syndrome, including prominent ear lobes, broad and flat nasal bridge, a single prominent tooth at the center of the bottom gum line, long palpebral fissures with upward curvature at the lateral edges, prominent finger pads, and noted neurodevelopmental delay. A whole exome sequence confirmed a pathogenic mutation in the *KMT2D* gene (AD, Heterozygous, variant c.5269C>T and p.R1757X) at 2 years of age.

Treatment

During her admission to the NICU after birth, she required a glucose infusion rate of 6 mg/kg/min to maintain a normal BG level. Subsequently, diazoxide (6 mg/kg/day) and chlorothiazide (13 mg/kg/day) were started, with good response. She was discharged home on diazoxide and chlorothiazide.

At 2 months of age, due to an admission secondary to respiratory failure associated with pulmonary hypertension, diazoxide was discontinued and she was able to maintain stable blood glucose levels with enteral feeds every 2 hours and continuous feeds overnight. At 11 months of age, she developed hypoglycemia while the gastroenterology team was trying to space her feeds. We attempted to manage her hypoglycemia by adding cornstarch 1 gm/kg to her bolus feeds every 2 hours. Initially, the patient responded well and was able to maintain euglycemia. After a few days, she developed diarrhea. Therefore, the cornstarch was discontinued and replaced by maltodextrin. Continuous glucose monitoring and fingerstick BG levels were utilized for close BG surveillance and appropriate titration of maltodextrin. Given her prior intolerance of cornstarch, we started at a low maltodextrin dose. Starting dose was 0.2 gm/kg of carbohydrates (5 mL of maltodextrin = 1.8 grams of carbohydrates) added to every other bolus feed, for a total of 3 bolus feeds (5 mL maltodextrin per feed). Using a goal BG of between 70 and 100 mg/dL, we titrated the dose accordingly. The patient's maximum maltodextrin dose to date has been 0.5 gm/kg of carbohydrates (15 mL of maltodextrin) with every bolus feed, for a total of 6 bolus feeds. Maltodextrin has been directly mixed with her formula and given through the G-tube. Maltodextrin never had to be added to overnight continuous G-tube feeds, which ran for 11 hours.

Outcome and Follow-up

The patient has been in regular follow-up with multiple specialties, including genetics, gastroenterology, nephrology, neurology, pulmonology, and endocrinology. She is currently receiving 0.3 gm/kg of carbohydrates (10 mL of maltodextrin) with her bolus feeds of toddler formula, 3 times a day. She also receives continuous feeds of toddler formula without maltodextrin via G-tube for 6 hours overnight. Solid food has slowly been incorporated into her diet with good tolerance.

During the evaluation in our clinic at 11 months old, her weight was between the 3rd and 5th percentile. Rapid weight gain was observed in the following months, secondary to more frequent feeds and the addition of maltodextrin. At 2 years of age, her weight for length was above the 97th percentile (standard growth charts). Gastroenterology team decreased the quantity of formula and calories, accordingly. At 3 years of age, her height and weight were at the 25th and 50th percentile (standard growth charts), respectively. Weight for length was at the 60th percentile for age.

Her blood glucose levels have been mainly in the range of 70 to 100 mg/dL, prior to feeds. Her family has opted to return to fingerstick BG checks twice per day, since BG values have been stable. Since 5 months of age, she has had no further admissions for hypoglycemia. She has never had any seizures, staring spells, or behavioral arrests. She attends a specialized daycare center where she receives speech-language therapy, occupational therapy, and physical therapy. At roughly 3 years old, she was walking and running independently, starting to speak in phrases, and able to feed herself. We are closely monitoring for other potential endocrine dysfunction associated with KS (growth, puberty, and thyroid disorders).

Discussion

Hyperinsulinism in the neonate may present as an isolated finding or manifest in various genetic syndromes [1]. KS is a more recent addition to the list of genetic syndromes associated with HH [4]. KS is classically caused by a pathogenic mutation in either the *KMT2D* or *KDM6A* gene. Heterozygous mutations in the *KMT2D* gene are responsible for more than 75% of KS, with most being de novo [4]. Almost 30% of patients with clinical features of KS do not carry mutations in either gene, and other genes have been associated with Kabuki-like phenotypes [5].

Patients with KS can present with a wide phenotypic spectrum. The most consistent features include the typical facial appearance, skeletal anomalies, dermatoglyphic abnormalities, some form of intellectual disability, and inadequate postnatal growth. Genetic testing has aided in creating a more expansive phenotypic spectrum for KS, with potential associated findings in multiple organ systems. The genotype-phenotype correlation continues to grow as clinicians and scientists identify and diagnose more patients with KS [3]. HH is rarely seen in KS, partly secondary to underdiagnosis and underreporting [1, 3].

We presented the case of a now 3-year-old girl with *KMT2D*-associated KS followed in our endocrine clinic for persistent hypoglycemia secondary to hyperinsulinism. HH has been classically associated with *KDM6A* mutations. Persistent hypoglycemia is a rare finding beyond the neonatal period but is a more common finding in *KDM6A*-associated KS [6]. Hyperinsulinism as a cause of hypoglycemia is presumed to be secondary to dysregulated insulin secretion. *KMT2D* and *KDM6A* are histone modifiers and are critical in embryogenesis and normal organ development, including pancreatic beta-cell formation. How exactly this translates

to hyperinsulinism in *KMT2D*-associated KS is not well-understood. The mechanism of the hyperinsulinism is more well-described in *KDM6A*-associated KS [3, 4, 6]. Possible explanations include altered beta-cell development, enhanced pancreatic beta-cell proliferation, and inappropriate increase in insulin secretion [3, 4, 6].

KS may not be easily identified in neonates and infants because the characteristic facial features may not yet be distinct [1]. A high index of suspicion should be maintained while evaluating a patient with hypoglycemia who has potential clinical manifestations of KS.

KS associated with hyperinsulinism is often diazoxide responsive, which is typically the first line of treatment [4]. Our team was unable to continue treatment with diazoxide secondary to development of pulmonary hypertension, forcing us to focus on dietary interventions. Potential nutritional treatment options include frequent feeds or adding complex carbohydrates in the form of cornstarch or maltodextrin, the latter of which is generally more tolerable [7, 8]. Close monitoring of BG values and titration of therapy is critical to optimize neurodevelopmental outcomes. Our team utilized both continuous glucose monitoring (CGM) and fingerstick BG values to guide therapy. CGM use has been shown to have a high false positive rate for detecting hypoglycemia in patients with hyperinsulinism [9]. Therefore, it is important to confirm hypoglycemia with a fingerstick to avoid overtreatment of low BGs or unnecessary escalation of therapy.

To our knowledge, our case represents one of the rare reported cases of HH in *KMT2D*-associated KS. Nutritional therapy was key to successful management when diazoxide had to be discontinued.

Learning Points

- Consider KS as a cause of HH, especially when suggestive clinical features are present.
- Persistent HH can be seen in *KMT2D*-associated KS.
- Addition of complex carbohydrates is a potential treatment in patients who cannot receive diazoxide.

Contributors

M.N.S. and P.G. were involved in the diagnosis and management of this patient and manuscript submission. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

No potential conflicts of interest relevant to this article were reported.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's parent.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Mısırlıgil M, Yıldız Y, Akın O, Odabaşı Güneş S, Arslan M, Ünay B. A rare cause of hyperinsulinemic hypoglycemia: Kabuki syndrome. *J Clin Res Pediatr Endocrinol*. 2021;13(4):452-455.
2. Subbarayan A, Hussain K. Hypoglycemia in Kabuki syndrome. *Am J Med Genet Part A*. 2014;164A(2):467-471.
3. Barry KK, Tsaparlis M, Hoffman D, *et al*. From genotype to phenotype—a review of Kabuki syndrome. *Genes (Basel)*. 2022;13(10):1761.
4. Salguero MV, Chan K, Greeley SAW, *et al*. Novel KDM6A Kabuki syndrome mutation with hyperinsulinemic hypoglycemia and pulmonary hypertension requiring ECMO. *J Endocr Soc*. 2022;6(4):bvac015.
5. Wang Y, Li N, Su Z, *et al*. The phenotypic spectrum of Kabuki syndrome in patient of Chinese descent: a case series. *Am J Med Genet A*. 2020;182(4):640-651.
6. Gole H, Chuk R, Coman D. Persistent hyperinsulinism in Kabuki syndrome 2: case report and literature review. *Clin Pract*. 2016;6(3):848.
7. Demirbilek H, Hussain K. Congenital hyperinsulinism: diagnosis and treatment update. *J Clin Res Pediatr Endocrinol*. 2017;9(Suppl 2):69-87.
8. Xu A, Cheng J, Sheng H, *et al*. Clinical management and gene mutation analysis of children with congenital hyperinsulinism in south China. *J Clin Res Pediatr Endocrinol*. 2019;11(4):400-409.
9. Rayannavar A, Elci OU, Mitteer L, De León DD. Continuous glucose monitoring systems: are they useful for evaluating glycemic control in children with hyperinsulinism? *Horm Res Paediatr*. 2019;92(5):319-327.