

# Novel *KDM6A* Kabuki Syndrome Mutation With Hyperinsulinemic Hypoglycemia and Pulmonary Hypertension Requiring ECMO

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## Abstract

Kabuki syndrome (KS) is a multisystem disorder estimated to occur in 1:32 000 newborns. Pathogenic mutations cause the majority but not all cases of KS in either *KMT2D* or *KDM6A*. KS can be suspected by phenotypic features, including infantile hypotonia, developmental delay, dysmorphic features, congenital heart defects, and others. Still, many of these features are not readily apparent in a newborn. Although neonatal hypoglycemia has been reported in 8% to 10% of patients with KS, the incidence and severity of hyperinsulinemic hypoglycemia (HH) is not well-studied. We present a full-term female infant with HH who was responsive to low-dose diazoxide. At 3 months of age, she was admitted for septic shock, worsening respiratory status, and severe pulmonary hypertension, requiring extracorporeal membrane oxygenation support. Her neonatal history was notable for hypotonia, dysphagia with aspiration requiring gastrostomy tube placement, and a cardiac defect—hypoplastic aortic arch requiring aortic arch repair. She has characteristic facial features, including prominent eyelashes, long palpebral fissures, and a short nasal columella. Next-generation sequencing for HH revealed a de novo likely pathogenic missense variant in *KDM6A* gene: c.3479G > T, p.Gly1160Val that was absent from population databases. Genetic testing for causes of HH should include testing of the KS genes *KMT2D* and *KDM6A*. Early detection of the underlying genetic defect will help guide management as all reported HH cases associated with KS have been responsive to diazoxide. Affected infants with underlying cardiac conditions may be at higher risk of serious respiratory complications such as pulmonary hypertension.

**Key Words:** hyperinsulinism, hypoglycemia, diazoxide, Kabuki syndrome, pulmonary hypertension

### Established Facts and Novel Insights

#### Established Facts

- Kabuki syndrome (KS) can be due to pathogenic variants of *KMT2D* or *KDM6A* genes, among others.
- One of the endocrine manifestations of KS, presenting in the neonatal period, is hyperinsulinemic hypoglycemia.
- Diazoxide is considered first-line therapy for treatment of hyperinsulinemic hypoglycemia and carries risks of fluid retention and pulmonary hypertension.

#### Novel Insights

- Hypoglycemia in the newborn period should raise consideration of genetic testing for KS especially as other associated clinical features may not be as apparent in the newborn period.

- This patient has a *KDM6A* sequence change, c0.3479G > T, in exon 24, resulting in an amino acid substitution, p.Gly1160Val. This de novo variant is absent from population databases.
- Abnormal cardiac physiology, such as hypoplastic aortic arch, in KS may lead to pulmonary hypertension. With further exacerbation by diazoxide, this can cause significant pulmonary decompensation.
- Patients and families should be given a “sick day” action plan in the case of hyperglycemia while on diazoxide therapy.

Kabuki syndrome (KS) is a multisystem disorder estimated to occur in 1:32 000 newborns [1]. The 5 cardinal clinical features of KS include craniofacial/skeletal anomalies, dermatoglyphic abnormalities (such as persistent fingertip pads), dysmorphic facial features, intellectual disability, and postnatal growth restriction [2]. In 2018, an international expert panel proposed that the diagnosis of KS can be definitively made in individuals with a history of infantile hypotonia, developmental delay, and/or intellectual disability, in

addition to 1 or both of the following: a pathogenic or likely pathogenic variant *KMT2D* or *KDM6A* and/or typical dysmorphic features [1]. Characteristic dysmorphic features of KS include long palpebral fissures and a short columella with depressed nasal tip; however, many of these phenotypic features are not readily apparent in a newborn, making the diagnosis of KS difficult at birth [1].

Endocrine manifestations of KS include growth hormone deficiency, hypothyroidism, and premature thelarche. Hypoglycemia (HH), which may be more clinically apparent in the neonatal period, has also been reported in patients with KS. However, the incidence and severity of HH in KS is not well-studied. Diazoxide is considered first-line therapy for treatment of HH. However, diazoxide can have adverse effects such as fluid retention and pulmonary hypertension (PH).

### Case Report/Case Presentation

An appropriate for gestational age female infant was delivered at 38 and 5/7 weeks via normal spontaneous vaginal delivery with APGARs 4 and 8 at 1 and 5 minutes, respectively. The delivery was complicated by meconium stained amniotic fluid and respiratory distress requiring nasal continuous positive airway pressure and admission to the neonatal intensive care unit (NICU). Starting at 1 hour of life, she was noted to have recurrent HH ranging from 34 to 68 mg/dL, which persisted despite intravenous fluids with glucose infusion rate up to 18.5 mg/kg/minutes and oral ad libitum feeds. On day of life (DOL) 3, laboratory assessment revealed serum glucose of 31 mg/dL with substantial elevation in insulin (19.2 mU/mL) and c-peptide (2 pmol/mL) and suppressed beta-hydroxybutyrate (<0.10 mmol/L), consistent with hyperinsulinism. Growth hormone (12.19 ng/mL) and cortisol (14.9 µg/dL) levels were reassuring. On DOL 6, a transthoracic echocardiogram (TTE) was done to establish the patient's cardiopulmonary status and showed hypoplastic aortic arch, patent ductus arteriosus, patent foramen ovale, and a perimembranous ventricular septal defect. To manage her hyperinsulinism, diazoxide was started at 5 mg/kg/day the same day after clearance by cardiology, and the dose was later increased to 8 mg/kg/day. Thiazide diuretic was also started. She was weaned off of dextrose containing intravenous fluids and transitioned to bolus feeds.

At 2 weeks of age, she underwent aortic arch repair and patent ductus arteriosus ligation with uneventful recovery. However, she continued to require oxygen supplementation due to frequent desaturations on room air. A subsequent TTE showed mild PH with half systemic right ventricular pressures despite being on furosemide and chlorothiazide. Diazoxide was discontinued (DOL 36), and then her nasal oxygen was weaned off to room air. Her blood sugar levels again dropped repeatedly, as low as 44 mg/dL, while on bolus feeds, so a lower dose of diazoxide (5 mg/kg/day) was resumed, along with furosemide. Her blood glucose levels again normalized on the lower dose of diazoxide. A limited genetic panel assessing for changes in the most common genes associated with hyperinsulinism (*ABCC8*, *GCK*, *KCNJ11*) was negative. She remained in the NICU due to feeding intolerance and eventually required gastrostomy tube placement. She was discharged home on diazoxide and furosemide at 3 months of age following a successful 6-hour safety fast (nadir of 59 mg/dL at 3 hours with spontaneous recovery).

Within 2 weeks of discharge, she presented to the emergency room with fever, dyspnea, hyperglycemia (glucose >500), tachycardia to 220 beats per minute, desaturations to 70%, hypotension, and hypoperfusion. Diazoxide was held due to PH and hyperglycemia. Home glucometer readings showed gradual increase in blood glucose levels, reaching levels of hyperglycemia the four days prior to admission. Caregiver attention was centered on notifying primary care with HH; hyperglycemia was not reported. Her clinical picture was concerning for sepsis requiring fluid resuscitation. In the pediatric intensive care unit, she had worsening respiratory failure, requiring intubation, nitric oxide, and inotropic support. Echocardiography features were significant for severe PH and decreased biventricular function with pericardial effusion without tamponade. She was placed on veno-arterial ECMO to avoid further deterioration and possible cardiac arrest. Despite diuresis, tamponade physiology worsened, and pericardiocentesis was performed; ECMO support was weaned off within 3 days. She was then weaned off inhaled nitric oxide and milrinone and subsequently extubated; however, low-dose sildenafil was started due to persistent PH. A repeat TTE 2 weeks later showed normal biventricular systolic function and no evidence of significant PH.

Because of the possible association of diazoxide with PH, management of her HH no longer included diazoxide. While being transitioned from total parenteral nutrition to enteral feeds, intravenous dextrose was used to maintain normal glucose levels. She ultimately did well on a regimen of continuous gastrostomy tube feeds for 8 hours overnight and enteral bolus feedings every 3 hours throughout the day. She was discharged home with normal blood sugars on furosemide and chlorothiazide, sildenafil, and instructions for routine glucose checks.

Further genetic testing was completed at the University of Chicago Genetic Services Laboratories (<https://dnatesting.uchicago.edu>), where a comprehensive congenital hyperinsulinism sequencing panel revealed a likely pathogenic variant in the *KDM6A* gene, which is associated with KS. No other variants were found in the 13 other genes in the panel, which also includes deletion/duplication analysis of all 14 genes. The *KDM6A* sequence change, c0.3479G > T, in exon 24, results in an amino acid substitution, p.Gly1160Val. This sequence change was not detected in either parent and was thus confirmed to be de novo in our patient. The p.Gly1160Val variant affects a highly conserved residue located in a known functional domain of the *KDM6A* protein and was predicted to be deleterious using several in-silico pathogenicity prediction tools (SIFT, PolyPhen2, Align GVGD, REVEL). This de novo variant was also absent from population databases (gnomAD, ExAC). Several of the patient's clinical features have been described as part of KS including hypotonia, feeding difficulties, and developmental delay, as well as characteristic facial features (long palpebral fissures and a short nasal columella). The p.Gly1160Val variant in *KDM6A* was thus deemed to be likely pathogenic according to American College of Medical Genetics and the Association for Molecular Pathology guidelines [3].

### Discussion

Congenital hyperinsulinemic HH in the neonate may present as an isolated finding or as a clinical feature of a syndrome. To date, mutations in at least 11 genes have been identified as

causal for hyperinsulinemic HH. The majority of monogenic HH cases are related to inactivating mutations in *ABCC8* and *KCNJ11* [4, 5]. KS is a more recent addition to a growing list of genetic syndromes associated with HH, most notably Beckwith-Wiedemann syndrome but also Turner syndrome, Sotos syndrome, and several others. However, potential mechanisms of syndromic hyperinsulinism remain poorly understood. In a recent analysis of 70 studies, only 4% of patients with KS were reported to have HH as a presenting feature [1, 2]. Despite this, KS has become the second most common syndromic cause of hyperinsulinism, following Beckwith Wiedemann, suggesting the possibility that HH may previously have been underrecognized or unreported in KS cases [6]. The majority of KS cases are caused by pathogenic mutations in either *KMT2D* or *KDM6A*, 2 genes that encode proteins used for chromatin transcription. Pathogenic mutations in these genes impair normal histone methylation resulting in abnormalities across multiple organ systems, likely due to alterations in gene expression regulated by imprinting control regions such as the 11p15 locus associated with Beckwith-Wiedemann syndrome and adjacent to *KATP* genes [2, 7]. Mutations in the *KMT2D* gene are autosomal dominant and are responsible for more than 75% of KS. *KDM6A* is X-linked and mutations may be inherited from an unaffected carrier female; however, most KS-associated genetic mutations are de novo rather than inherited [8].

Our patient presented with hyperinsulinemic HH on DOL 1. This finding corresponds with recently published observations by Hoermann et al that the onset of HH in children with KS is observed mainly in their neonatal period [9]. Of note, our patient has a pathogenic variant in *KDM6A*, which appears to be more commonly associated with HH than *KMT2D* mutations [9, 10]. Diazoxide responsiveness helps to clarify the possible mechanism of *KDM6A* mutation found in our patient. *KDM6A* codes for a demethylase that acts on H3K27 and induces a steady state in proliferating cells. A proposed hypothesis for hyperinsulinism in KS is the dysfunction of demethylation of the H3K27 protein leading to the deregulation of beta cell development [11]. There is an increase in the number of H3K27me3 domains in the endocrine pancreatic cells during differentiation in vivo [12]. Loss of *KDM6A*-associated demethylation of the H3K27me3/me2 mark may lead to enhanced pancreatic beta-cell proliferation, leading to hyperinsulinism [13].

Early diagnosis of KS is not only helpful for predicting the likelihood of HH response to diazoxide therapy [14] but is also essential for guiding evaluation of other associated features such as the cardiac defects in our patient, as well as ongoing assessment and intervention for developmental delay. Hyperinsulinemic states, which decrease glucose and ketone bodies in the brain, jeopardize optimal neurocognitive development, which is of critical importance in children already at risk for such struggles [15].

While HH related to *ABCC8* and *KCNJ11* mutations is often resistant to diazoxide, KS-associated hyperinsulinism is often diazoxide-responsive [4, 5]. Diazoxide works by binding to the sulfonyleurea receptor 1 subunit of the adenosine 5'-triphosphate-sensitive potassium (*KATP*) channel to keep it open, preventing insulin secretion from the pancreatic beta cell [4]. Although diazoxide is usually very effective at reducing insulin secretion, it should be used with caution. Fluid retention is a relatively common side effect of diazoxide and may partially explain an apparent associ-

ation with PH, particularly in patients with underlying cardiac pathology [16]. In a retrospective cohort study of 295 patients on diazoxide therapy, 2.4% showed signs of PH on TTE between 2 to 317 days after diazoxide initiation, with most of these patients having a history of structural cardiac abnormalities and/or prematurity [16]. Of note, none of those subjects had echocardiograms before initiation of diazoxide available for review to confirm that PH was not present prior to diazoxide initiation.

During our patient's NICU course, she was found to have hypoplastic aortic arch physiology, which can lead to slightly increased pulmonary artery pressures and may have contributed to her later decompensation. In addition to her history of aortic coarctation repair, during her readmission, she was found to have a worsening pericardial effusion that further complicated her course. A case series of 10 patients with KS and HH showed that despite having cardiac anomalies including atrial and/or ventricular septal defects, most patients (9/10) did well on diazoxide without pulmonary sequelae [2]. Another study demonstrated a much lower risk for severe adverse events (SAE) including PH associated with diazoxide use in those with genetic HH (3.6% with any SAE, 1.2% with PH) as compared to those with perinatal stress hyperinsulinism (16.7% with any SAE, 7.6% with PH) [17]. Currently, there is limited evidence on diazoxide dosing strategies, but the expert consensus of the members of the Drug and Therapeutics Committee of the Pediatric Endocrine Society emphasized the importance of reducing diazoxide dose if hyperglycemia occurs [18]. It thus remains unclear in our patient to what extent the low dose of diazoxide may have contributed to her decompensation, which was very likely primarily related to her underlying cardiopulmonary pathology.

We report a case with KS who presented with diazoxide-responsive HH during the neonatal period, which was later complicated by PH in the setting underlying cardiopulmonary anomalies and acute infection. HH in the newborn period should raise consideration of genetic testing for KS especially as other associated clinical features may not be as apparent in the newborn period.

This case also emphasizes the importance of patient and family education regarding glucose monitoring while on diazoxide, particularly during times of illness. Hyperglycemia should prompt medical attention and dose reduction or temporary cessation of diazoxide, with particular concern when respiratory distress occurs. Patients with underlying cardiac abnormalities should have periodic and/or episodic echocardiograms while on diazoxide therapy for early detection of PH. Further research is needed to delineate subgroups at greatest risk of adverse complications and clarify protocols for glucose and cardiac treatment and monitoring.

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## Author Contributions

M.V.S. and K.C.: clinical diagnosis, data collection, writing the main draft of this article. U.D: following up the patient, clinical diagnosis, and editing of the manuscript. S.A.W.G. and D.W.: genetic analyses and reviewing and editing of the manuscript. D.d.G. and M.H.: genetic analysis. T.R. and M.L.: following up the patient, clinical diagnosis, editing, and verifying data in the article.

## Disclosures

The authors have nothing to disclose.

## Statement of Ethics

Written informed consent was obtained from the parent guardian of the patient for publication of this case report.

## Data Availability

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

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