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Case Report

Diazoxide-related Hyperglycemic Hyperosmolar State in a Child With Kabuki Syndrome

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Abstract

Diazoxide is a commonly used first-line medication for the treatment of hyperinsulinism. Hyperglycemia may occur with diazoxide use. However, hyperglycemic hyperosmolar state (HHS) secondary to diazoxide is an exceedingly rare but potentially life-threatening adverse effect. We present a case of a 2-year-old with Kabuki syndrome and hyperinsulinism on diazoxide. She presented with 4 days of fever, respiratory symptoms, and lethargy. She was influenza B positive. Initial workup indicated HHS, with an elevated serum glucose (47.1 mmol/L [847.8 mg/dL]; reference range 3.9-6.0 mmol/L; 70-108 mg/dL), serum osmolality (357 mmol/kg H_2O; reference 282-300 mmol/kg H_2O) but absent urine ketones and no metabolic acidosis (venous pH 7.34). Her course was complicated by an acute kidney injury. Management in the hospital included discontinuation of diazoxide and intravenous fluid resuscitation, following which hyperglycemia and hyperosmolarity resolved. No insulin therapy was required. She remained normoglycemic without diazoxide for 2 weeks but subsequently required restarting of diazoxide for hypoglycemia. This case highlights the need for early recognition and prompt management of diazoxide-related HHS to reduce negative outcomes. We present the first case report of a child with Kabuki syndrome and hyperinsulinism with diazoxide-induced HHS.

Key Words: diazoxide, hyperosmolar hyperglycemic syndrome, hyperinsulinism, Kabuki syndrome

Introduction

Hyperinsulinism, the most common cause of persistent hypoglycemia in children, is characterized by low serum glucose and inadequate ketone production due to dysregulated insulin secretion. Recurrent and profound hypoglycemia in children with hyperinsulinism can result in neurological sequelae, including neurodevelopmental delay and epilepsy (1). Hyperinsulinism is a known feature of Kabuki syndrome, a rare inherited disorder characterized by typical facial features, skeletal anomalies, intellectual disability, and growth deficiency. Kabuki syndrome possibly accounts for up to 1% of patients diagnosed with congenital hyperinsulinism (2, 3).

Diazoxide is a first-line pharmacotherapy in the management of pediatric hyperinsulinism. Adverse effects include hypertrichosis, sodium and water retention, pulmonary hypertension, neutropenia, thrombocytopenia, hyperuricemia, and potentially necrotizing enterocolitis (1, 4). Given its effect on increasing glucose levels, diabetes ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are potential risks of diazoxide. However, diazoxide-induced HHS is exceedingly rare in children. To our knowledge, only 4 prior case reports exist in the literature (5-8).

We describe the diagnostic evaluation and management of a 2-year-old with hyperinsulinism and Kabuki syndrome who presented with HHS and compare this to previously reported cases.

Case Presentation

We present the case of a 2-year-old with Kabuki syndrome diagnosed at 45 days of life through whole exome sequencing. Her medical history included hyperinsulinism, atrial and ventricular septal defects, gastro-jejunal tube-dependent feeding, solitary ectopic kidney, vesicoureteral reflux with recurrent urinary tract infections, and chronic hypernatremia, likely secondary to chronic kidney disease. She was diagnosed as a neonate with presumed transient hyperinsulinism due to multiple risk factors (prematurity, gestational diabetes, and macrosomia) and hypoglycemia requiring a high glucose infusion rate (14.5 mg/kg/min). Confirmatory laboratory testing was not collected at the time. She was temporarily managed with diazoxide, which was discontinued prior to discharge from the hospital early in life due to resolution of the hypoglycemia. Subsequently, at 12 months of age, she had biochemical-confirmed hyperinsulinism while fasting secondary to gastro-jejunal tube intussusception, with a critical sample demonstrating hypoglycemia (serum glucose 2.6 mmol/L [46.8 mg/dL] [reference range 3.9-6.0 mmol/L; 70-108 mg/dL]) with inappropriate insulin secretion (insulin 13 pmol/L [1.87 mIU/L] [reference range 9-297 pmol/L; 1.23-42.77 mIU/L]). She required persistent diazoxide at a low dose (3.75 mg/kg/day) until presentation to the hospital. Notably, her hyperinsulinism responded well to conventional treatment and did not require additional therapy required for children with dysregulated insulin secretion from gastric-jejunal tube feeds. She presented to the emergency

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department with 1 day of lethargy and 4 days of fever, cough, rhinorrhea, and post-tussive emesis in the context of sick contacts. No home glucose monitoring was completed for 2 days before presentation, although notably previous self-reported capillary blood glucose indicated no dysglycemia.

On examination, she was irritable, toxic, and dehydrated. She had tachycardia (heart rate 141 beats/min), fever (38.0 °C), tachypnea (29 breaths/minute), and hypoxia requiring 2 L/min low-flow oxygen. She had no hypotension, altered mental status, or focal neurologic symptoms.

Diagnostic Assessment

Biochemistry on presentation noted significant hyperglycemia (serum glucose 39.3 mmol/L [707.4 mg/d]), with confirmation on repeat sample (serum glucose 47.1 mmol/L [847.8 mg/dL]). Subsequent investigations demonstrated hyperosmolarity (corrected serum sodium 166 mmol/L [reference range 135-145 mmol/L], serum osmolality 357 mmol/kg H_2O [reference range 282-300 mmol/kg H_2O]), without ketosis (urine ketones negative) or metabolic acidosis (venous blood gas: pH 7.34, bicarbonate 39 mmol/L). She had an acute-on-chronic kidney injury (creatinine 92 umol/L [1.04 mg/dL]; baseline 60-74 umol/L [0.68-0.84 mg/dL]; reference range 16-35 umol/L [0.18-0.4 mg/dL]) without significant electrolyte derangements (potassium 3.4 mmol/L [reference range 3.5-5.0 mmol/L], phosphate 1.33 mmol/L [reference range 1.46-2.29 mmol/L]). Normal serum creatine kinase (193 U/L) (reference range 60-305 U/L) did not suggest rhabdomyolysis. Hemoglobin A1c (HbA1c) was 5.0% (31 mmol/mol), with no prior HbA1c available for comparison.

Treatment

Diazoxide was held and HHS was managed with intensive fluid resuscitation and frequent biochemistry monitoring. She received 20 mL/kg normal saline (NS) bolus followed by 40 mL/hour (1.5 times maintenance rate) of hypotonic fluids (0.2NS with D5W and 0.45NS with 10 KCl). No insulin infusion was required. Following 36 hours of treatment, her acute kidney injury and HHS resolved with serum glucose 5.0 mmol/L (90 mg/dL), corrected serum sodium 149 mmol/L (baseline 140-149 mmol/L), and creatinine 72 umol/L. Feeds were advanced to her home regimen without further hyperglycemia, while chronic hypernatremia was managed with additional free water.

Additionally, her infectious disease workup was positive on nasopharyngeal swab for influenza B. Her urine and blood cultures were negative. She received 7 days of ceftriaxone for presumed concurrent bacterial pneumonia. Her respiratory status improved without oxygen requirements at discharge.

Outcome and Follow-up

As she maintained normoglycemia in the hospital on home feeds, diazoxide was not restarted. She passed a 6-hour fast off diazoxide and was discharged with outpatient endocrinology follow-up. However, 2 weeks post-discharge, she developed recurrent hypoglycemia (lowest capillary glucose 2.1 mmol/L [37.8 mg/dL]), and diazoxide was reinitiated at 3.75 mg/kg/day. To monitor for recurrent HHS, the parents were instructed to ensure home capillary blood glucose monitoring at least twice daily pre- and after resuming feeds. She has since remained normoglycemic.

Discussion

We present a rare case of a patient with Kabuki syndrome and persistent hyperinsulinism, presenting with diazoxide-induced HHS in the context of influenza B infection.

HHS is a manifestation of severe hyperglycemia and hyperosmolarity. Diagnostic criteria for HHS in children includes serum glucose > 33.3 mmol/L (> 600 mg/dL), serum osmolality > 320 mOsm/kg H_2O without significant acidosis (venous pH > 7.25 or bicarbonate >15 mmol/L), or ketosis (β-hydroxybutyrate < 1.5 mmol/L or urine ketones negative to small) (9). Pediatric HHS has a high mortality rate between 20% and 60% (10). HHS complications in children include severe electrolyte disturbances (hypokalemia, hypophosphatemia, hypocalcemia), rhabdomyolysis and secondary acute kidney injury, malignant hyperthermia, ventricular arrhythmias, thrombosis, worsening mental status, and death (9, 10). While patients with HHS experience significant intravascular depletion and hyperosmolar state, translocational hyponatremia/normonatremia may be present due to the dilutional effects and extracellular fluid shifts from profound hyperglycemia. Failure to appreciate the severity of the hyperosmolar state and free water deficit and calculate corrected sodium may lead to inappropriate management, including choice of fluids (11).

Pediatric incidence of HHS in patients with type 2 diabetes is reportedly 2% (9). In contrast, diazoxide-induced HHS is even more rare in children. There have been 4 prior cases described in the literature (Table 1). One case involved a presumed mixed HHS/DKA presentation (7). Another involved Cornelia De Lange syndrome and suggested furosemide use may have contributed to HHS (8). Our case is the first reported case of diazoxide-induced HHS in a child with Kabuki syndrome.

Although home capillary glucose monitoring was not performed in our patient in the preceding days before hospitalization, her presentation was more likely an acute process given her normal HbA1c during admission and prior normoglycemia over the past year on stable low-dose diazoxide (3.75 mg/kg/day).

Multiple potential mechanisms may explain her HHS. First, diazoxide acts on the β-cell sulfonylurea receptor-1 subunit of outward-rectifying K-ATP channel, causing membrane hyperpolarization and inhibition of calcium-dependent insulin secretion (12). However, a secondary "hit" may have contributed to her presentation. Specifically, infection-related upregulation of proinflammatory cytokines and counterregulatory hormones, including cortisol, catecholamines, and glucagon, stimulate glycogenolysis and gluconeogenesis, promoting increased hepatic glucose output, peripheral insulin resistance, and ultimately hyperglycemia (13). Coupled with diazoxide-related relative insulin deficiency, these mechanisms may have resulted in HHS. Three of 4 prior case reports noted similar presentations of diazoxide-induced HHS in the context of infection (5, 7, 8). While other medications (eg, glucocorticoids, atypical antipsychotics, calcineurin inhibitors, and thiazide diuretics) could promote hyperglycemia (14), this patient was importantly not taking other predisposing medications. Additionally, although case reports describe

Table 1. Prior case reports of diazoxide-induced HHS

Parameters	Case 1 (Balsam et al, 1971) (5)	Case 2 (Savage et al, 1977) (6)	Case 3 (Mangla et al, 2018) (7)	Case 4 (Nakazawa et al, 2021) (8)
Patient demographics	13-month-old male	17-week-old male	16-month-old male	5-year-old female
Pertinent prior diagnoses	Diazoxide-responsive hyperinsulinism, GTCS, developmental delay	Diazoxide-responsive hyperinsulinism, obesity, hypotonia	Diazoxide-responsive hyperinsulinism, developmental delay	Diazoxide-responsive hyperinsulinism, Cornelia de Lange syndrome, VUR, aortic regurgitation
Diazoxide dose	7.5 mg/kg/day	15 mg/kg/day	15-20 mg/kg/day	5 mg/kg/day
Age at diazoxide initiation	13 months	16 weeks	4 months	Unspecified
Presentation	1 week post diazoxide initiation, developed upper respiratory tract infection Presented with comatose state, GTCS, and pinpoint pupils No prior polyuria or anorexia Cardiorespiratory arrest following admission	HHS occurring 10 days post diazoxide initiation	Fever, poor feeding, polyuria tachypnea, multiple GTCS	Tachycardia, polyuria, and fever
Pertinent investigations	Serum glucose: 111.1 mmol/L (2000 mg/dL) Sodium: 128 mmol/L Plasma osmolality: 367 mOsm/kg H_2O Serum acetone negative Blood culture: Hemophilus influenzae	Serum glucose: 24 mmol/L (432 mg/dL) Sodium: 154 mmol/L Plasma osmolality: 352 mOsm/kg H_2O Urea: 25 mmol/L	Serum glucose: > 22.2 mmol/L (400 mg/dL) Sodium: 154 mmol/L Creatinine: 97.3 umol/L VBG: pH 7.04, bicarbonate 8.3 mmol/L Serum ketones: 1.1 mmol/L HbA1c: 5.7% (39 mmol/mol)	Serum glucose: 29.4 mmol/L (529 mg/dL) Sodium: 160 mmol/L ABG: pH 7.4, bicarbonate 31.9 mmol/L Plasma Osmolarity: 357 mOsm/kg H_2O HbA1c 5.8% (40 mmol/mol) Urine culture: E. coli
Management	IV hypotonic fluids (7 mL/kg/hr) IV insulin (1.2 U/kg/hr) Diazoxide held 11 days, then restarted (4 mg/kg/day) IV ampicillin	IV 0.45 NS (rate unspecified), subcutaneous insulin (4 units once) Diazoxide held 36 hours, then restarted (9 mg/kg/day)	IV NS fluids (40 mL/kg bolus, unspecified subsequent rate) IV insulin (0.1 U/kg/hr) Diazoxide held 4 days, then restarted (20 mg/kg/day) Intubated and ventilated, inotropes, antibiotics, valproate	IV extracellular tonic fluids (20 mL/kg bolus, then 8 mL/kg/hour) No insulin administered Diazoxide held 9 days, then restarted (5 mg/kg/day) Furosemide discontinued
Outcomes	Despite normoglycemia, persistent developmental delay, and ongoing neurodeficits 4 months post-discharge	Despite normoglycemia, persistent hypotonia, and unresponsiveness Death at 7 months secondary to respiratory infection	Rhabdomyolysis, spastic quadriparesis, developmental regression	Resumption of diazoxide secondary to failed fasting challenge Post-discharge, remained normoglycemic

Values in parentheses are conventional units.

Abbreviations: ABG, arterial blood gas; GTCS, generalized tonic-clonic seizures; HbA1c, hemoglobin A1c; HHS, hyperosmolar hyperglycemic syndrome; IV, intravenous; NS, normal saline; VBG, venous blood gas; VUR, vesicoureteral reflux.

an association of diabetes with Kabuki syndrome in adulthood (15), to our knowledge, no prior literature describes this association in children or the association of Kabuki syndrome and HHS in children or adults. Lastly, her history of chronic hypernatremia, which may be multifactorial in the context of chronic renal disease as well as potential chronic volume contraction, may have exacerbated her clinical presentation.

In conclusion, we present a rare side effect of diazoxide-induced HHS and the first report in a child with Kabuki syndrome. Although such adverse effects are uncommon, given the high morbidity and mortality attributed to HHS, we advocate for providers to have a low threshold for diagnostic evaluation of HHS in children on diazoxide with significant hyperglycemia and/or clinical or biochemical features suggestive of HHS. This is especially prudent in children with concurrent infections. Rapid diagnosis and targeted management of HHS through aggressive fluid resuscitation and gradual normalization of hyperglycemia and hyperosmolarity are critical to ensure favorable outcomes in these children.

Learning Points

- HHS is a rare but potential adverse effect of diazoxide, including in those with Kabuki syndrome.
- Early recognition and management of HHS in patients on diazoxide, especially with concurrent infections, may reduce significant morbidity and mortality associated with HHS.
- Distinguishing HHS from DKA is important given differences in management; HHS requires more aggressive rehydration with insulin initiation only once a stable decline of glucose is achieved.
- To ensure early detection, children on diazoxide should have regular glucose monitoring, and families should be advised to monitor for hyperglycemia symptoms, especially during illness.

Contributors

All authors made individual contributions to authorship. H.K., J.S., C.Li., and C.La. were involved in diagnosis and management of the patient. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient's relatives or guardians.

Data Availability Statement

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

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